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A STUDY OF EXPERIMENTAL METHODS FOR PRODUCING THROMBOSIS IN SMALL ARTERIES

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ONE OF THE GREATEST DRAWBACKS to the surgery of small arteries, such as the coronary, cerebral, and smaller vessels of the extremities, is the high incidence of thrombosis following surgical manipulation of these vessels. A number of reports have appeared suggesting measures for the prevention and treatment of thrombosis under these circumstances, but the results of these studies have shown considerable variance with one another. In working on this problem ourselves, it became apparent that one reason for the lack of accord in previous reports was the absence of any uniform method that would consistently reproduce an experimental thrombus.

Many techniques for the production of experimental thrombosis in both veins and arteries have been reported. Each of these techniques proved unsatisfactory for studying the prevention and treatment of thrombosis in surgically traumatized small arteries for one or both of the following reasons. First, the method failed to produce consistent thrombosis and therefore gave no baseline with which to compare treatment. Second, the method did not simulate the conditions of mechanical trauma that exist during the surgery of small arteries, but rather produced thrombosis by some means totally unrelated to this clinical problem. A method is presented that overcomes both of these shortcomings and that has produced a suitable thrombus for the study of this problem. In a subsequent report, the results of treatment with anticoagulants, fibrinolytic agents, and other forms of therapy will be presented.

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METHODS

The following three methods were studied:

Method A. Ten mongrel dogs, all weighing 30 pounds or more, were used. Anesthesia was maintained by intravenous nembutal in this and all other methods.

The common femoral arteries were exposed and their diameters measured. Each vessel was carefully dissected free over a 2 centimeter segment, and all branches were divided and ligated with fine silk. Distally, a No. 3-0 plain catgut ligature was tied around both the vessel and a No.18 needle placed parallel and next to the vessel. The

TABLE I.—INCIDENCE OF THROMBOSIS FOLLOWING THROMBIN INJECTION—METHOD A

Follow-up period, days	*No. of vessels*	*Diameter of vessels, mm.*	*No thrombus*	*Nonoccluding thrombus*	*Occluding thrombus*	*Per cent occluded*
21	20	>3	9	2	9	45

TABLE II.—INCIDENCE OF THROMBOSIS FOLLOWING CHEMICAL INTIMECTOMY—METHOD B

Follow-up period, days	*No. of vessels*	*Diameter of vessels, mm.*	*No. of vessels patent*	*No. of vessels occluded*	*Per cent occluded*
1	24	2–3	8	16	67
2	4	2–3	1	3	75
4	4	2–3	0	4	100
6	4	2–3	2	2	50
8	4	2–3	0	4	100
10	4	2–3	1	3	75
12	4	2–3	1	3	75
14	4	2–3	0	4	100
Total	52		13	39	75

needle was then gently slipped out of the loop, and a constricting but nonoccluding ligature was left around the femoral vessel.

The previously dissected 2 centimeter segment just proximal to the ligature was then isolated between two bulldog clamps. By using a No. 24 needle, the blood in this segment was aspirated into a syringe containing 100 units of thrombin in 0.2 cubic centimeter of saline and rapidly reinjected into the same segment. After waiting 2 minutes, the bulldog clamps were removed to leave a firm 2 centimeter thrombus that was held in place by the partially constricting ligature. The wounds were closed with silk. Three weeks later, the dogs were reanesthetized, and the femoral vessels were removed for gross and microscopic study.

Method B. In 13 mongrel dogs, all weighing between 13 and 25 pounds, the common femoral and carotid arteries were exposed and their diameters measured. After all branches were divided and ligated over a 2 centimeter segment, this area was isolated by bulldog clamps. All blood was aspirated from this portion of the vessel, and it was filled with 0.1 normal sulfuric acid through a No. 20 needle. After 2 minutes, a second needle was placed at the opposite end of the segment, and the vessel was flushed with water for 5 minutes. Both needles and clamps were removed and temporary pressure was applied for hemostasis. Occasionally, a stitch had to be placed at each needle site to stop the bleeding. At varying time intervals from 1 day to 2 weeks, the dogs were reanesthetized, and the vessels were removed and examined grossly and microscopically.

Previous experiments in this laboratory have shown that this procedure completely destroys the intima that is exposed to the acid. After this treatment, the interior of the vessel wall consists of the internal elastic membrane or deeper layers of the media.

Method C. Twenty-five mongrel dogs weighing 12 to 41 pounds were used. The common femoral and carotid arteries were exposed, and each vessel was carefully dissected free over a 2 centimeter segment. All branches were clamped, divided, and ligated with fine silk. Temporary constricting ligatures were placed at each end of this segment for hemostasis, and a transverse arteriotomy was made at the distal end of the segment. The diameter of the vessel was measured. By means of a hypodermic needle with a bent point or a dental burr, the intima was thoroughly stripped out over a 2 centimeter segment. The arteriotomy was closed with No. 5-0 arterial silk. Upon release of the constricting ligatures at both ends of the isolated segment, arterial continuity was re-established with free flow of blood through the vessel. The wound was closed with silk. At intervals of from 1 day to 3 weeks after this procedure, the animals were reanesthetized, and the vessels removed, examined, fixed in formalin, and studied microscopically.

RESULTS

Twenty vessels in 10 dogs, in which thrombosis was attempted by thrombin injection (method A), showed a 45 per cent incidence of complete thrombosis when examined 3 weeks later (Table I). Two vessels (10 per cent) had a nonoccluding thrombus, and the 9 remaining vessels (45 per cent) showed no evidence of the thrombus formed at the first procedure.

Fifty-two vessels in 13 dogs, in which thrombosis was attempted by means of a chemical intimectomy (method B), showed a 75 per cent incidence of thrombotic occlusion when examined 1 to 14 days later (Table II). Thirteen, or 25 per cent of the vessels were not occluded. Twenty-four of the 52 vessels in this group were examined 1 day after chemical intimectomy. Of these 24 vessels, 16 (67 per cent) were totally occluded and 8 (33 per cent) were found to be open.

In 12 dogs weighing 30 to 41 pounds, in which 40 femoral and carotid vessels measuring greater than 3 millimeters in diameter were used, thrombosis was attempted by mechanical intimectomy (method C). When these vessels were examined 10 to 42 days later, 15 vessels (38 per cent) contained an occluding thrombus, and 25 vessels (62 per cent) had no thrombus (Table III).

In 20 dogs weighing 12 to 25 pounds, in which vessels measuring 2 to 3 millimeters in diameter were used, thrombosis was again attempted by method C. When the vessels were examined 1 to 21 days later, 68 (82 per cent) were totally occluded, and 12 (18 per cent) were patent. Of these 80 vessels, 20 were examined 1 day after intimectomy, and 19 of these 20 vessels (95 per cent) were thrombosed. Of the 68 vessels examined within 14 days after intimectomy, 61 (89 per cent) were occluded, but of the 12 vessels examined 21 days after intimectomy, only 7 (58 per cent) were thrombosed (Table IV).

TABLE III.—INCIDENCE OF THROMBOSIS FOLLOWING MECHANICAL INTIMECTOMY IN 12 DOGS WEIGHING 30 TO 41 POUNDS—METHOD C

Follow-up period, days	*No. of vessels*	*Diameter of vessels, mm.*	*No. of vessels open*	*No. of vessels occluded*	*Per cent occluded*
10	4	>3	2	2	50
21	28	>3	19	9	32
42	8	>3	4	4	50
Total	40		25	15	38

TABLE IV.—INCIDENCE OF THROMBOSIS FOLLOWING MECHANICAL INTIMECTOMY IN 20 DOGS WEIGHING 12 TO 25 POUNDS—METHOD C

Follow-up period, days	*No. of vessels*	*Diameter of vessels, mm.*	*No. of vessels open*	*No. of vessels occluded*	*Per cent occluded*
1	20	2–3	1	19	95
2	4	2–3	0	4	100
6	4	2–3	0	4	100
8	12	2–3	4	8	67
12	4	2–3	1	3	75
14	24	2–3	1	23	96
21	12	2–3	5	7	58
Total	80		12	68	82

DISCUSSION

In the search for a method to prevent thrombosis after arterial surgery, it must be kept in mind that there is no clear understanding of the basic cause of such thrombosis. What the precipitating factors are and how long the thrombogenic stimulus produced at operation will persist after surgery are not known. Since this is the case, it is important to use an experimental preparation that not only will produce consistent and standardized thrombosis for the purpose of comparison, but also will accomplish this through a thrombogenic stimulus that mimics clinical conditions as closely as possible. Only with such a preparation can it be expected that a regimen will be worked out in terms of therapeutic agents, dosage, duration of therapy, mode of application, and similar details that will be effective in preventing postoperative arterial thrombosis. Perhaps a more important advantage of a preparation that meets these two criteria is that it may be expected to help elucidate some of the unknown factors at work in the production of postoperative thrombosis.

On the basis of these criteria, methods A and B are considered inadequate. However, the results in Table IV indicate that method C, mechanical intimectomy, meets the criterion of consistently reproducible thrombosis in a high percentage of cases when applied to arteries less than 3 millimeters in diameter. This method also bears the closest resemblance to the clinical conditions existing after arterial surgery. In both the experimental and clinical situations the vessel is denuded of intima, and there are ragged intimal fragments and arterial suture lines producing turbulence and resistance to flow.

The data in Tables III and IV also verify the clinical impression that under given conditions of trauma and rate of flow, the tendency toward thrombosis increases as the caliber of the vessel decreases. Also, the rate of thrombosis decreases as the duration of follow up increases. Microscopic sections show that this fact is due to recanalization of the clots. Because of the high incidence or recanalization after 14 days, this method will be primarily useful in studying the prevention and treatment of thrombosis during the first 2 weeks following the thrombogenic stimulus.

The percentages of complete thrombosis after 24 hours when methods B and C were used were 67 and 95 per cent, respectively. The comparison is interesting, in that method B produced complete intimectomy with minimal mechanical trauma to the vessel, and method C produced the same result with extensive mechanical trauma. This observation suggests that although removing the endothelium from a vessel is a considerable stimulus to thrombosis, there are other factors brought into play by manipulating, squeezing, and suturing the artery that remain undefined. Whatever the nature of the thrombotic stimulus that is activated by mechanical trauma, its elucidation will be a helpful part of devising a means of preventing postoperative arterial thrombosis.

SUMMARY

1. A mechanical method of intimal destruction that will consistently produce arterial thrombosis is outlined.

2. It is suggested that this preparation may be useful in elucidating some of the unknown factors contributing to thrombosis following arterial surgery as well as in developing an effective means of prevention and treatment of this condition.

3. Two other methods that are less suitable for this study than the mechanical method are also presented.

THE COMPONENTS OF THE FIBRINOLYTIC SYSTEM IN A VENOUS SEGMENT UNDERGOING EXPERIMENTAL THROMBOSIS

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A PROPAGATING VENOUS THROMBUS may be obtained experimentally in the dog by means of the partial ligature of a venous segment without interruption of the blood flow, followed by the intravenous injection of homologous serum (2). Changes of various coagulation factors in the venous segment undergoing thrombosis have been reported previously (3). In the present article the behavior of the fibrinolytic system under the same experimental conditions is discussed.

There is fairly general agreement on the components of the fibrinolytic system but some discrepancy as to their nomenclature. The active enzyme is known as plasmin or fibrinolysin. This is formed when a precursor (plasminogen or profibrinolysin) is acted upon by an activator found in the blood and in many tissues. In turn, the blood activator is formed when a proactivator is acted upon by bacterial or tissue lysokinases (Fig. 1).

MATERIALS AND METHODS

Eight mongrel dogs, weighing from 10 to 12 kilograms, were used in this study. As described in detail previously (2), two partially constricting ligatures were placed approximately 2 inches apart on each jugular vein of the animals under pentothal anesthesia; then the dog received homologous serum intravenously—10 milliliters per kilogram of body weight—over a period of 10 minutes. A partly obstructing thrombus formed after the infusion in each of the partially ligated jugular segments which continued to propagate slowly for a period of several days. Samples of blood were drawn from the femoral veins and from each jugular vein above and below the thrombosing segment by means of 17 gauge needles attached to 3 centimeter long polyethylene tubes. The blood was collected into sterile test tubes coated with silicone and containing the anticoagulant solution. To study the effects of stasis alone the first samples were taken after placement of the ligatures and immediately preceding the serum infusion. Other samples were taken at the end of the serum infusion and, in some cases, 15 minutes, 30 minutes, 1 hour, and 24 hours afterward. Plasma was separated by centrifugation at 2,000 revolutions per minute for 10 minutes. In some instances aliquots of blood were collected in glass test tubes and allowed to clot. Results with serum closely paralleled those with plasma and are not reported herein.

The samples of plasma were tested for over-all fibrinolytic activity; plasmin, plasminogen, activator, proactivator, and antiplasmin activities. The fibrin plate technique of Astrup and Mullertz was used in all instances because of familiarity with this method. Nine milliliters of 0.35 per cent bovine fibrinogen in veronal buffer at *p*H 7.8 and 0.15 molar solution were transferred to Petri's dishes of an average diameter of 10 centimeters. The solution was then coagulated with the addition of 0.3 milliliter of thrombin containing 30 National Institute of Health units. The plates were either used

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as such or heated at 85 degrees C. in a hot air oven for 35 minutes to destroy plasminogen and other components of the fibrinolytic system. Three-hundredths milliliter drops of each specimen to be tested were placed on a plate which was incubated in a hot air incubator at 37 degrees C. for 18 hours. The relative areas of lysis were obtained by measuring representative perpendicular diameters with calipers and obtaining their product. It was confirmed during the course of this work that the lytic areas were better outlined and more consistent results were obtained if several drops of bromothymol blue (0.04 per cent in 95 per cent ethyl alcohol) were added to the fluid of the lysed areas. A drop of 10 per cent sodium hydroxide solution was sometimes added for color contrast. The surface tension of the alcohol of the dye made lysed area edges more clear and regular.[1]

The test materials for each constant were as follows: Fresh oxalated plasma was used in studying the over-all fibrinolytic activity. To test plasmin activity, 1 milliliter of plasma was diluted to 20 milliliters with distilled water. Five-hundredths of acetic acid was added to a *p*H of 5.1 to 5.2. The dilution was chilled to 5 degrees C. and centrifuged. The precipitate, which contains plasminogen and plasmin spontaneously formed with the removal of the inhibitors, was dissolved in 1 milliliter of veronal buffer (*p*H 7.8) (euglobulin fraction). The same fraction was also used in preparation of the reagent for the testing of plasminogen and proactivator activity. To evaluate plasminogen activity, 0.5 milliliter of the euglobulin fraction was incubated 1 hour at room temperature with 0.1 milliliter of human activator to convert plasminogen to plasmin. The human activator was prepared by mixing equal volumes of streptokinase—10,800 units per milliliter—and human euglobulin. Human plasma was used for the preparation of activator of plasminogen because human plasma, unlike dog and beef plasma, is rich in proactivator. To test for activator, the untreated plasma was added to fibrin plates which were unheated and thus represented an abundant source of plasminogen. To test for proactivator, 0.2 milliliter of the euglobulin fraction was incubated for 1 hour at room temperature with 0.2 milliliter of a solution made up of veronal buffer (*p*H 7.8), containing 2,160 units of streptokinase and 6 milligrams of fibrinogen. The excess of streptokinase converted the proactivator to activator. In turn, the activator converted the plasminogen (present in excess in the fibrinogen) to plasmin. The values obtained, of course, did not take into account the spontaneous loss of plasmin during the period of incubation in the conversion of plasminogen to plasmin, in the incubation of antiplasmin with plasmin, or in the incubation period in the proactivator determination. To study antiplasmin (inhibitor) activity, 0.2 milliliter of plasma was incubated 1 hour at room temperature with 0.2 milliliter of a standard plasmin solution and then plated. Ratnoff and associates have shown that there are at least 3 inhibitors in human serum, one destroyed by heating at 56 degrees C. for 30 minutes, a second heat stable but inactivated by ammonia, and a third not destroyed by heat or ammonia. Others may be present. In our test, we assumed that all were separated from the plasmin by the precipitation of the latter at *p*H 5.1 to 5.2 and that all were operative under our experimental conditions of incubation for an hour with plasma and plasmin at room temperature and the subsequent incubation on Astrup plates.

RESULTS

The effects of anesthesia seemed negligible in all instances, although erratic.

[1]Conversion of area values to linear values (D.J.S.). The following considerations should be kept in mind in evaluating the findings presented. The areas of lysis on the fibrin plates do not bear a simple arithmetic ratio to the degree of lytic activity, i.e., the concentration of plasmin. Rather, the logarithms of the areas of lysis on the fibrin plates are proportional to the logarithms of the plasmin concentration. Thus, in an attempt of statistical analysis, the crude areas of lysis were converted to percentage values of increment by means of a graph which had been constructed by comparing the areas of lysis and a series of dilutions of standard plasmin. Also values were calculated by the least squares formula of Snedecor, a more accurate method than preparation and inspection of a graph. Although theoretically more accurate, it was found that curves drawn from the latter values were not essentially different from those drawn from the crude areas of lysis. These are used for our illustrations as being closer to the original data.

Plasmin (Fig. 2a). The activity of plasmin in the samples of blood from the general circulation and from the area above the ligature rose at the end of the infusion of serum and for at least 15 additional minutes. Values were back in the range of normal within 30 minutes after the completion of the infusion and definitely normal 1 hour later. In the segment below the ligature the initial plasmin concentration was higher and became strikingly elevated after the infusion of serum, still remaining higher 1 hour later. The 24 hour samples showed approximately equal plasmin activity in all areas, notwithstanding the continued propagation of the thrombus.

Plasminogen (Fig. 2b). The determination of plasminogen activity involved more variables than for plasmin; yet the results obtained were quite consistent. Findings in the samples from the general circulation and from the segment above the ligature were similar. The effects of the ligature alone were equivocal. The infusion of serum was followed by significant elevation of the plasminogen activity. After a rebound, possibly due to the activation of plasminogen to plasmin and lasting for at least 1 hour, all values had returned to normal within 24 hours. Blood samples from below the thrombosing segment gave the most interesting results. The activity of plasminogen was far below that in blood from other areas which indicated that plasminogen was disappearing from the blood in the thrombosing segment presumably by conversion to plasmin. This effect was still quite evident 1 hour after the end of the serum infusion. The 24 hour specimens showed approximately the same plasminogen activity for all samples.

Activator. Tests for plasminogen activator were uniformly negative. It should be pointed out, however, that the plasmin produced by any activator present might have been insufficient to counterbalance the antiplasmin present in the samples of plasma.

Proactivator. The values obtained for proactivator activity were quite consistent. Values for the general circulation were practically unchanged during the infusion but rose slightly afterward. The values above the thrombus showed only slight changes. The proactivator activity in blood collected below the thrombus was slightly elevated at the end of the infusion but dropped moderately below the original value 1 hour later.

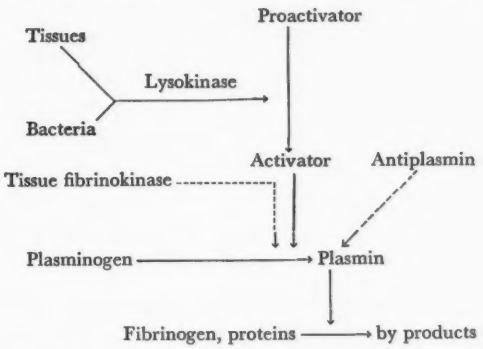

FIG. 1. Outline of the fibrinolytic system in man.[2]

Antiplasmin (Fig. 2c). As calculated by preliminary experiments, the activity of antiplasmin in the blood prior to the infusion was equivalent to approximately 3 times that of plasmin. Changes observed were insignificant.

Gross fibrinolytic activity. No untreated plasma sample showed any lytic activity on the heated fibrin plates.

DISCUSSION

It is generally understood that the formation of an intravascular clot is followed by increased and sustained fibrinolytic activity either in the circulating blood or at least at the site of thrombus formation. Our findings seem to have considerable bearing on the correctness of this hypothesis, even if ample reservations should be made for the fact that available methods are still relatively in-

[2]The basic step is the activation of plasminogen (profibrinolysin) to plasmin (fibrinolysin). This is accomplished either by tissue fibrinokinases, or through the action of the blood activator. The blood activator, in turn, is derived from the proactivator through the action of lysokinase found in tissues or in bacteria (streptokinase). Inhibitors are present for each phase of this mechanism. The mechanism as described is essentially similar in man and dog with the exception that the activity of proactivator is very low in serum and plasma of dog. Accordingly the activation by streptokinase is poor. Nevertheless we have been able to demonstrate the presence of proactivator activity in dog serum, which is somewhat in discrepancy with findings of other authors.

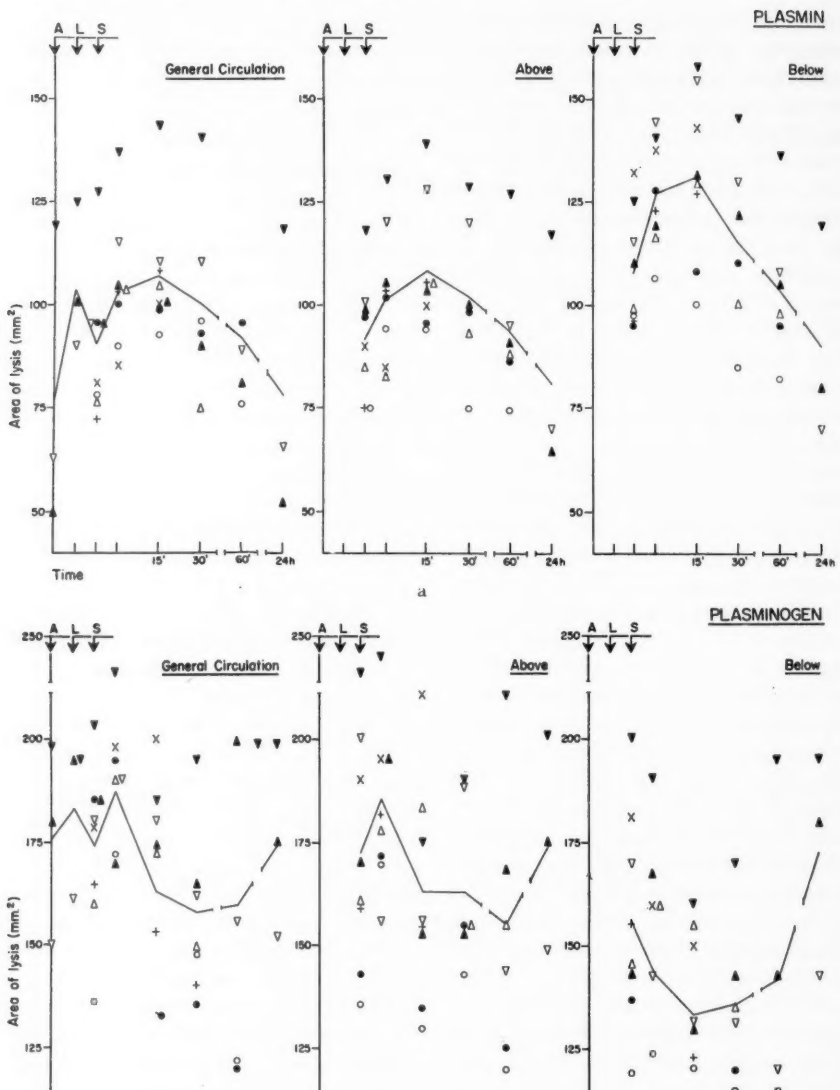

FIG. 2. Behavior of some of the components of the fibrinolytic system during the formation and propagation of a thrombus: a, plasmin (fibrinolysin); b, plasminogen (profibrinolysin).

adequate and results are often poorly reproducible. This is particularly true in the study of serum antiplasmin activity because the method of determination is fairly insensitive.

At least in our experimental conditions, the initiation of clotting in a venous segment was promptly followed by activation of the fibrinolytic system. The rapidly reversed

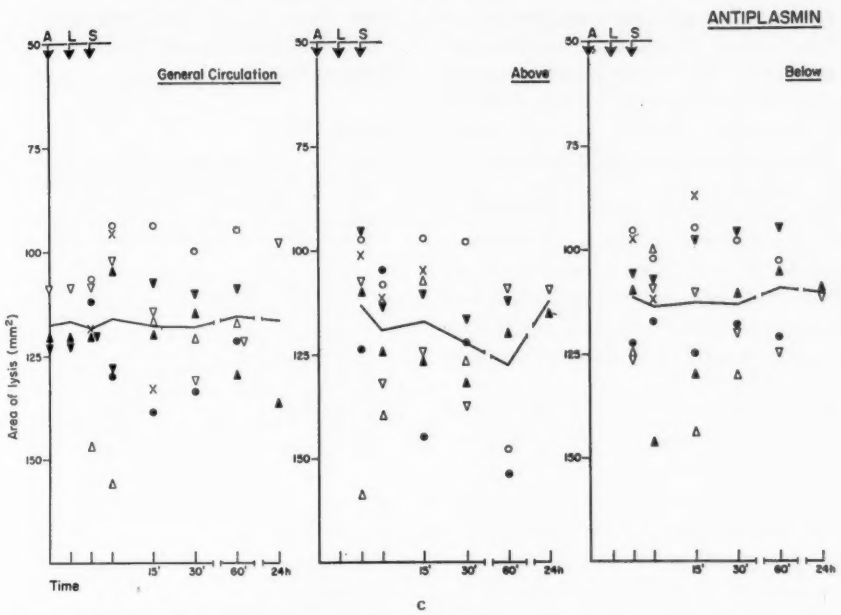

FIG. 2 (continued). c, Antiplasmin (antifibrinolysin). Each graph contains data for these constants in the general circulation, samples of blood collected above the partial ligature and below the partial ligature. Values are expressed as areas of lysis calculated by direct measurement.

changes observed in the blood collected from the general circulation and from the area above the ligature might have represented only a fleeting reaction to the state of hypercoagulability induced by the administration of serum. On the other hand, the increased activity of plasmin and the decreased activity of plasminogen were of considerably greater intensity in the samples of blood collected from below the thrombosing segment and suggested a true activation of the fibrinolytic system in the area of thrombosis. As changes observed in the activity of proactivator and activator were negligible, the mechanism of activation was not entirely clear. The action of thrombin which forms continuously at the site of intravascular clotting and is able to activate the fibrinolytic system at least in vitro might have been significant.

In any case, the activation of plasmin was a fleeting phenomenon even below the area of thrombosis. Twenty-four hours after initiation of thrombosis, even as the clot continued to propagate, the fibrinolytic mechanism was dormant in all areas of the circulation. Thus, the initiation of venous thrombosis appeared accompanied by activation of the fibrinolytic system, mostly at the local level. This phenomenon, however, was only transitory as any excess of plasmin activity was quickly controlled by antiplasmin. The conclusion appears inescapable that, at least in the dog, activation of the fibrinolytic system provided only a fleeting defense against the initiation of a thrombus and a very ineffectual one against its propagation.

SUMMARY

1. The components of the fibrinolytic system were studied in a group of 8 dogs in which a propagating thrombus had been produced by combined partial ligature and injection of homologous serum.

2. There were no significant changes of

proactivator, activator, and antiplasmin activity. The lack of response in antiplasmin might have been due to the poor sensitivity of the methods employed. The activity of plasmin increased slightly in the initial phase of formation of the thrombus but returned to normal within 60 minutes in samples of plasma from the general circulation and from the segment above the thrombosing segment. It remained elevated for at least 1 hour but not longer than 24 hours in the samples of blood collected below the area of thrombosis. Plasminogen behaved in a reciprocal manner.

3. Thus, a slight activation of fibrinolysis occurred in the phase of initiation of thrombosis. It was not sustained and appeared ineffectual in the control of the propagation of the thrombus.

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IRRADIATION AND SURGERY IN THE TREATMENT OF BRONCHOGENIC CARCINOMA

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THE CURABILITY of any cancer is determined largely by its own natural history. The type of cancer which, unpredictably, remains localized for long periods of time without producing either extensive local infiltrations or distant metastases is a highly curable cancer; conversely, the type of cancer which spreads early and widely by the lymph or blood stream is a cancer which is seldom curable. Cancer of the lung, one of the most common of all cancers in the human male, belongs to this latter group. The absolute cure rate for all patients, treated or untreated, is around 5 per cent in most centers where large numbers of patients with bronchogenic carcinoma have been studied.

If it is to be of value, cancer therapy should be suited to the largest number of patients affected by the disease, even those with advanced disease.

For many years it has been known that irradiation can sterilize some bronchogenic carcinomas. This mode of therapy has been applied usually only in inoperable tumors, in patients who are considered poor operative risks, and in patients who have refused operation. In resectable tumors, operation has been the treatment of choice.

There is considerable evidence that irradiation can reduce the local vitality of most bronchogenic carcinomas as shown either by a marked reduction of the tumor size or its rate of growth; it will make large masses disappear and in some cases will sterilize the whole tumor. Out of a series of 171 patients so treated by Smithers, 4 per cent were alive without disease at 5 years. There are many isolated cases published in the literature in which the tumor was completely sterilized, at operation or at autopsy, after treatment by irradiation. There have been few attempts in large unselected series of patients to study the results of irradiation in operable tumors. Preoperative irradiation has been used in small groups of patients or in isolated cases by Trump, Bromley, and others. Furthermore, a serious attempt has not been made in a large series of cases to study the effects of radical irradiation not only upon the primary bronchogenic tumor but also upon the lymph node metastases of the mediastinum and scalene and supraclavicular areas. With the advent of supervoltage therapy—1 to 24 million volts or cobalt teletherapy—and modern techniques, it is possible to irradiate the whole of the lung tumor and the lymph node-bearing areas of the mediastinum and scalene and supraclavicular regions and to deliver a cancerocidal dose to these areas, as described by Trump, Schulz, Buschke, and Watson.

More than 3 years ago we decided to explore the action of cobalt teletherapy in bronchogenic carcinoma and to explore especially the possibilities of an approach combining cobalt teletherapy and surgery in the treatment of carcinoma of the lung. The scope of this study was: (1) to demonstrate the feasibility of radical therapy by cobalt 60 teletherapy of the primary tumor and mediastinal and supraclavicular areas by delivering a 5,500 to 6,000 roentgen tumor dose in 5 weeks; (2) to demonstrate that a radical operation could be performed after

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radical cobalt treatment without increasing the rate of postoperative complications to undesirable levels; (3) to gather all possible information of the action of radical irradiation upon the primary tumor of the lung and its metastases in the mediastinal and supraclavicular areas; (4) to determine whether some cases considered nonresectable by conventional criteria could be rendered resectable; (5) to study the effects of this combined therapy upon survival, incidence of metastases, and recurrences.

From the study of the present status of the treatment in bronchogenic carcinoma, several features are evident: (1) The cure rate is depressingly low. (2) The direct seeding of the tumor, histologic extension of the disease beyond the excised organ, and the production of distant metastases cannot be prevented by operation alone. (3) When mediastinal nodes are involved, operation alone yields a poor cure rate. (4) When scalene and supraclavicular nodes are involved operation does not cure the patient. (5) There is no curative therapy available with our present knowledge when the patient has distant metastases. (6) There is not a chemical therapeutic agent consistently effective in controlling bronchogenic carcinoma.

A definite gain could be achieved if it were demonstrated that present day irradiation could consistently sterilize a reasonable percentage of primary tumors and of lymph nodes enclosed in the treatment area before operation. The cure rate could be increased under the following conditions: (1) if tumors inoperable because of extension into the carina, trachea, large vessels, and chest wall, or if mediastinal or supraclavicular nodes could be made operable; (2) if direct seeding and distant metastases produced by surgical manipulation could be diminished or avoided; (3) if more cases of mediastinal lymph node metastases could be controlled; (4) if some patients with scalene or supraclavicular lymph node metastases could be cured; (5) if the cure rate could be increased with less selection of patients.

In instances in which complete sterilization of the tumor is not attained, it is reasonable to assume that the possibilities of seeding will be greatly diminished because of the poor vitality of heavily irradiated cells. It is assumed that sterilization by irradiation will never be 100 per cent of all cases and that operation will always remain a necessary and important part of treatment. It is possible that with a combined approach a curative treatment could be applied to more patients with less selection and with increased chance of success.

The objections to combined cobalt-surgical therapy are: (1) the development of metastases under therapy or during the waiting period; (2) the possible increase in the number of operative and postoperative complications; (3) the length and expense of a strenuous treatment for both the hospital and the patient.

The technique of treatment now in progress consists of irradiation by cobalt 60 teletherapy, followed by a waiting period of 2 months, and then surgical removal of the lesion. The technique of irradiation has been designed to take the maximum advantage of the knowledge of the natural history of the disease. In a single volume of irradiation, the primary tumor and its most probable extension are treated in continuity. The minimally treated area is the primary site and the whole mediastinum. A source of cobalt 60 of 1,000 curies of 1.5 centimeter diameter at a minimum of 50 centimeters skin target distance is used. The source is mounted for rotational therapy with a 55 centimeter radius. The dosimetry is individually calculated for each patient. Careful localization films are taken prior to the treatment and are checked by portal films obtained under treatment conditions with the same cobalt unit.

In all techniques, irradiation of the unaffected lung is carefully avoided to prevent a reduction in breathing capacity. Pulmonary function studies are carried out before irradiation and again prior to operation. Three different techniques are used

depending upon the histologic type and location of the tumor.

1. For well-differentiated squamous cell carcinomas and adenocarcinomas the treatment is: (a) The whole mediastinum, from the sternal notch to at least 6 centimeters below the carina, is treated in continuity through the same field of irradiation which includes the primary; 4,500 roentgen tumor dose in 4½ weeks by stationary irradiation is so delivered. The site of the primary and any other detectable tumor in the mediastinum are given an additional 1,500 roentgen tumor dose in 1 to 1½ weeks by means of rotation whenever possible. (b) If the unilateral or bilateral scalene node biopsy is positive, both supraclavicular areas are treated, also in continuity with the primary and mediastinal fields; a 5,000 roentgen given dose is delivered in 4 weeks over these areas. (c) If the patient presents clinically or histologically positive supraclavicular lymph node metastases, the supraclavicular areas are treated as in (b) plus an additional 1,000 roentgen given dose to the site involved by the metastases.

2. For anaplastic tumors or undifferentiated squamous or adenocarcinomas the arrangements of the field for treatment are: (a) The primary tumor and the mediastinum are delivered a 4,000 roentgen tumor dose in 4 weeks. An additional 2,000 roentgen tumor dose in 1½ to 2 weeks is delivered to the area of the primary and any other detectable tumor of the mediastinum, preferably by rotation. (b) In all cases both supraclavicular areas are treated, even in the absence of any evidence of metastases; 5,000 roentgen given dose in 4 weeks is again the dosage. One thousand roentgens more are added in the involved site if either the supraclavicular or the scalene biopsy is positive.

3. For primary tumor in the apex of the lung the primary tumor is treated in continuity with the mediastinum, the supraclavicular areas, and the upper portion of the homolateral axilla; 5,000 roentgen tumor dose is delivered in 5 weeks. The fields are reduced to cover only the residual tumor and the adjacent mediastinum, and an additional 1,000 roentgen tumor dose is given in 1 week.

In general, the treatment has been well tolerated. In most instances, the general condition of the patient improves under therapy. The cough, pain, or hemoptysis usually subsides after the second week of treatment. Some patients have complained of esophagitis near the end of the treatment, others of mild pharyngolaryngitis when the supraclavicular areas were treated. The reaction of the skin to irradiation never goes beyond an erythema or dry peeling. The radiographic changes in the lung are sometimes dramatic. After the first 2 weeks of therapy an entire atelectatic lung may clear or a large tumor mass may disappear after a 4,000 roentgen tumor dose is delivered. The radiographic changes do not always parallel the histologic results. In 3 of our patients the tumor or the lung cavitated during or after the treatment. One of the 3 cases of cavitation was due to a Friedländer infection involving the lung mostly outside of the irradiated area, necessitating emergency pneumonectomy at a later date. The other 2 patients underwent a routine pneumonectomy at the end of the prescribed waiting period.

The 2 month postirradiation waiting period is indispensable if fullest advantage is to be taken of this type of combined therapy. This period is considered a time in which most of the irradiation effect has been achieved in the tumors of the lung. It also allows sufficient time for the acute reaction of radiation to subside. If operation is performed earlier, bleeding may be increased because of the congestion characteristic of the acute radiation reaction. If it is performed after this period, postirradiation fibrosis may make the operation, and probably the healing, more difficult.

All patients with bronchogenic carcinoma without distant metastasis are submitted to combined therapy. If an exploratory thoracotomy is necessary to prove the diagnosis

of neoplasm, the primary tumor and mediastinal nodes are biopsied and outlined with silver clips. Cobalt 60 therapy is begun 7 to 10 days later.

Operation is performed 2 months after the high voltage therapy is completed. In most instances a pneumonectomy is performed through a posterolateral thoracotomy incision. Adhesions are usually minimal except in those patients in whom thoracotomy was performed previously for biopsy. The tissue planes during the hilar dissection are somewhat thicker but there is no true fibrosis or excessive bleeding. Closure of the bronchial stump is performed by a single layer of interrupted silk sutures. The bronchial stump is often left uncovered.

The tissues marked by clips are always removed at the second operation for histologic study. The chest wall is closed tightly without drainage. During the postoperative recovery period there have been no complications which could be attributed directly to the previous cobalt 60 therapy.

ANALYSIS OF OUR EXPERIENCE

Our material consists of 52 patients. Twenty-six of these were under the direct control of the Division of Radiotherapy and the Division of Thoracic Surgery at the University of Maryland Hospital, and combined therapy was planned as soon as the diagnosis was established. The remaining group consists of patients from other hospitals and from private physicians whose patients were not under our complete control. Eighteen patients in this group received cobalt teletherapy alone. Eight other patients without previous irradiation were operated upon in other hospitals and were treated by us postoperatively with irradiation, the same mediastinal and supraclavicular technique already described being used.

A comparison of these groups presented some difficulty because of elements of selection which are impossible to eliminate.

Series I—planned combined therapy. This series considered for combined therapy consisted of 26 patients. Only 9 patients had early disease; 13 patients had inoperable tumors, 9 of which were considered unresectable upon exploratory thoracotomy, and the remainder were considered inoperable on clinical grounds; 7 patients had mediastinal lymph node metastases proved by biopsy. Eighteen patients received the complete combined treatment, and the remaining 8 patients did not have postirradiation operation either because distant metastases developed or because they refused operation. All of these 18 patients had a positive biopsy from the primary lesion, and 3 of these patients also had a positive biopsy from the lymph node metastases. All patients were operable and resectable after cobalt teletherapy (8 of the 18 patients were considered inoperable before cobalt teletherapy). The surgical procedure was pneumonectomy in 17 cases and lobectomy in 1 case.

Pathologic analysis of the surgical specimens after the completion of treatment, including biopsy of all available mediastinal glands, showed: 1 patient had active tumor cells in the primary lesion and in the mediastinal nodes; 6 patients had residual active tumor cells in the primary tumor and negative mediastinal nodes; 1 patient had negative cells in the primary lesion and positive cells in mediastinal nodes; and 10 patients had no histologic evidence of active tumor in either primary or nodes.

The primary lesion, when removed surgically, contained residual active tumor cells in 39 per cent of the 18 cases; the mediastinal lymph nodes, in 11 per cent.

Of the 3 patients from whom a positive biopsy was obtained from the mediastinal nodes, 2 were found free of tumor in mediastinal nodes at the time of the second operation.

The survival rates to date of the 18 patients who underwent the combined cobalt-surgical treatment are as follows:

1 Patient died of massive uncontrolled contralateral pneumothorax on the third postoperative day.

1 Patient died 5 months after operation with an acute myocardial infarction.

1 Patient died at 18 months of uncontrolled disease and generalized metastases. This patient showed uncontrolled tumor in both the mediastinal nodes and primary site at operation.

1 Patient is alive with distant metastasis 22 months after the completion of treatment. One year after the completion of treatment this patient was found to have a tumor of the right kidney which was removed. The pathologist believes that the bronchogenic tumor was metastatic from the tumor of the kidney.

1 Patient is alive 16 months postoperatively with distant metastases.

13 Patients are alive and well without clinical or roentgenologic evidence of tumor. The survival times are 1 patient for 44, 25, 24, 20, 19, and 18 months, respectively. The remaining 7 patients are now alive for more than 10 months without evidence of further disease. Two patients are too recent for evaluation (4 months).

Therefore, 15 out of 18 of these patients are alive today, 13 out of 18 are alive and well without evidence of tumor, and in 3 out of 18 of these metastases developed during this treatment.

The remaining 8 of the 26 patients for whom the combined therapy was planned but not performed yield the following results: Four of the patients refused operation after radiation. Four patients displayed metastases either during the irradiation treatment or while waiting for operation. Of these 8 patients, 5 are now dead with a survival period of 4 to 7 months; 3 of them still had an active primary lesion at the time of death. Three patients are still alive —for 16, 9, and 8 months, respectively, and 1 of these has a still active primary lesion.

Out of a series of 26 patients for whom combined radiation-operation therapy program was planned, there is a survival rate of 62 per cent.

Series II—patients having postoperative irradiation (surgery and cobalt teletherapy). There were 8 patients in this group. Two underwent lobectomy and 6 pneumonectomy under the care of other surgeons before being seen for irradiation therapy. Thus, these patients all had operable, clinically early lesions. All 8 patients had proved cancer cells in the primary tumor, and 7 had metastatic disease in the mediastinal nodes. One patient without biopsy from the mediastinal nodes had radiologic evidence of and clinical symptoms from mediastinal metastasis—vocal cord paralysis of recent appearance. In all cases except 1, the irradiation followed the operation shortly in the postoperative period, 10 to 14 days. Follow-up of these 8 cases shows that 5 of the patients are dead. Of these, 1 lived 12 months, the remainder died within 4 months of the beginning of the treatment. Four died with distant metastases. Three of the patients are alive and well without evidence of tumor for 7, 14, and 27 months, respectively.

Series III—patients having irradiation alone (cobalt teletherapy). There were 18 patients, 11 of whom were found to be inoperable, 5 because of previous exploratory thoracotomy and biopsy and the remaining 6 on clinical grounds. Seven of these patients had mediastinal metastases, and in 6 some symptoms of mediastinal compression were present. Fourteen of these patients have expired. One patient lived longer than 1 year while the others died within 8 months. Four patients are alive 2 to 6 months after therapy, 2 with active disease.

In 11 of this group of 18 patients, metastases developed, and 11 patients had clinical or autopsy evidence of failure to control the primary tumor in the bronchi.

Six patients of those who died achieved a good but short-lasting palliation.

COMMENTS

A comparison of the results among the three groups of patients is not possible because of the small number of cases and the disparity of the material. The group of patients who underwent postoperative irradiation is a selected group in the sense that all of the patients had mediastinal metastases. The group of patients treated by irradiation alone constituted those with more advanced disease. The group considered for combined cobalt 60 and surgery were not

early cases, however, since 50 per cent of these were considered inoperable.

Some interesting facts can be pointed out because of their possible significance in this study to date: (1) the high resectability rate after cobalt therapy; (2) the low incidence of mediastinal lymph node metastasis after irradiation; (3) the lower than anticipated incidence of distant metastases in the cases in which combined therapy was applied; (4) the lack of complications imputable to the combined procedures.

It is obvious that radical irradiation with cobalt teletherapy can be delivered for bronchogenic carcinoma which will encompass the primary tumor and its most common sites of extension, mediastinal and supraclavicular lymph node bearing areas, with good tolerance. This irradiation will be efficient in controlling the primary tumor and tumor within mediastinal nodes in a considerable number of cases. Radical operation has been possible in this series after irradiation treatment by telecobalt without increasing the rate of postoperative complications. The resectability rate is increased by preoperative irradiation.

This form of therapy has suggested the possibility of sterilizing mediastinal lymph node metastases by means of cobalt irradiation. The need for postirradiation operation to remove the site of the primary tumor is ever present because of failure in always controlling the primary tumor. Of the 44 patients treated by cobalt alone, and cobalt plus surgery, 21 of them had active disease at the site of the primary tumor.

It is believed that the evidence so far accumulated justifies pursuing this study.

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ESOPHAGEAL VARICES PRODUCED EXPERIMENTALLY IN THE DOG

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To study the factors influencing the development and progression of esophageal varices and the relationship of this process to changes in portal blood flow and blood pressure, an experimental model of the naturally occurring disease is needed. Previous attempts to achieve this end have been singularly unsuccessful in the dog. The difficulty appears to stem largely from the exceptional ability of the dog to develop an extensive extraesophageal collateral circulation in response to portal venous occlusion. The present study outlines the various methods employed to produce esophageal varices experimentally. It will be shown that esophageal varices and sustained portal hypertension may be readily induced in the dog when the flow in the obstructed portal system is amplified by an arteriovenous shunt. The implications of these experimental findings will be discussed in relation to the naturally occurring disease.

MATERIALS AND METHODS

Mongrel dogs of both sexes weighing between 20 and 25 kilograms were used for this study. In the early experiments, the portal or splenic vein on the hepatic side of the shunt was progressively occluded by means of a silk ligature or reactive cellophane tape, until the venous pressure reached approximately 40 centimeters of citrate.

Arteriovenous shunts were made between the splenic artery and vein on the splenic side of the coronary vein. The spleen was removed, the blood vessels were occluded by rubber shod bulldog clamps, and a side-to-side anastomosis measuring approximately 1.0 centimeter in length was made with a No. 6-0 monofilament nylon suture.

Aortoportal shunts were made by interposing an autologous graft, taken from the external jugular vein, between the anterior wall of the aorta and the right lateral wall of the portal vein in such a way that the venous valves were reversed.

Pressure measurements were made with a citrate manometer after cannulating a branch of the coronary or gastroepiploic vein. After measurements of pressure, an injection of 20 cubic centimeters of 50 per cent hypaque was made and a single roentgenogram was taken at the conclusion of the injection. In addition, postmortem injection studies were made with 90 per cent hypaque in several animals.

EXPERIMENTS

Esophageal varices produced by splenic arteriovenous fistula followed by progressive occlusion of the splenic vein. To obviate the problems experienced by previous investigators, it was believed that the increase in venous pressure should be localized to the fundus of the stomach rather than dissipated throughout the splanchnic venous system. Accordingly, the following groups of experiments were carried out.

Group 1. The spleen was removed and a side-to-side shunt was performed between the splenic artery and vein as described. A loose tie was then placed around the main splenic vein immediately proximal to its junction with the superior mesenteric vein. At a second stage operation performed approximately 1 month later, the silk tie was located and tied down to obstruct the splenic vein completely. Seven animals

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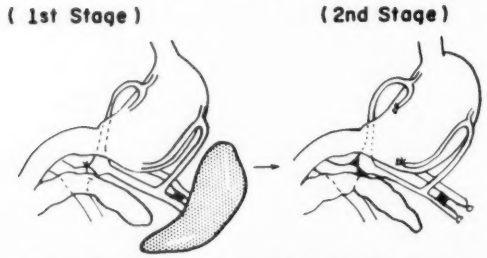
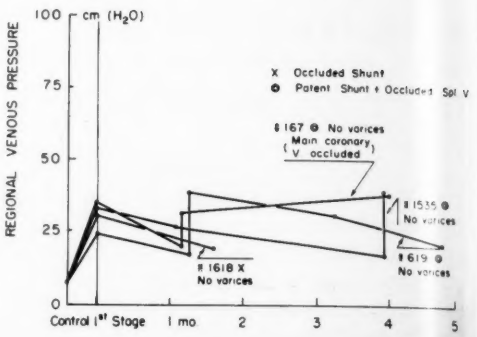


FIG. 1. Representative examples of animals in group 1. The procedure consisted of splenectomy, splenic arteriovenous shunt, and progressive occlusion of the splenic vein. The venous pressure remained below 40 centimeters of citrate, and no varices developed in this group.



survived for 2 to 8 months after completion of the second stage. Pressure measurements recorded in Figure 1 show that fundic venous pressure remained below 40 centimeters of citrate. No varices were found in this group, and careful study demonstrated that an extensive collateral circulation had developed through the veins in the tail and body of the pancreas as well as the omentum.

Accordingly, the second experiment was designed to overcome this problem.

Group 2. At the first stage, the spleen, the tail of the pancreas, and the greater and lesser omentum were removed and the right gastroepiploic veins were divided. A splenic arteriovenous fistula was made and the splenic vein was partly occluded in the manner described. At the second stage, performed approximately 1 month later, the splenic vein was completely occluded by a silk tie. The results are summarized in Figure 2a, b, and c. A number of animals died soon after the operation as a result of extreme passive hyperemia of the stomach often associated with gastrointestinal hemorrhage. Twelve animals were available for long term study. These constituted about one-third of the animals originally operated upon. In 6, the splenic vein was found to be completely occluded and the shunt patent. Esophageal varices and sustained venous hypertension were demonstrated in all of these animals. In addition, 3 animals were found to have varices of a lesser degree. In 2 of these, the shunt was patent but the vein was only partly occluded, and in the remaining case both vein and shunt were occluded. Representative examples illustrating these findings are shown in Figure 2. It should be noted that venous pressures greater than 40 centimeters of citrate were recorded in all animals in which extensive varices developed. In cases in which the fistula remained patent, sustained hypertension was recorded as long as 6 months after the initial operation.

Group 3. This experiment was designed to obviate the need for secondary occlusion of the splenic vein and consisted essentially of the group 2 operation in which a reactive cellophane band was substituted for the silk ligature around the splenic vein. This band was constricted down until the initial splenic venous pressure measured between 40 and 50 centimeters of citrate. The mortality rate in this group was extremely high because of rapid thrombosis at the site of application of the cellophane and extreme passive hyperemia of the stomach. The results of this study are summarized in Figure 3. Of the 4 animals surviving longer than 2 months, only 1 was found to have both a completely occluded splenic vein and a widely patent shunt. Portal pressure remained raised in this case, and melena was noted at 6 months. The presence of extensive esophageal varices was demonstrated by splenic venogram. In 2 of the remaining 3 animals, the shunt was found to be partly

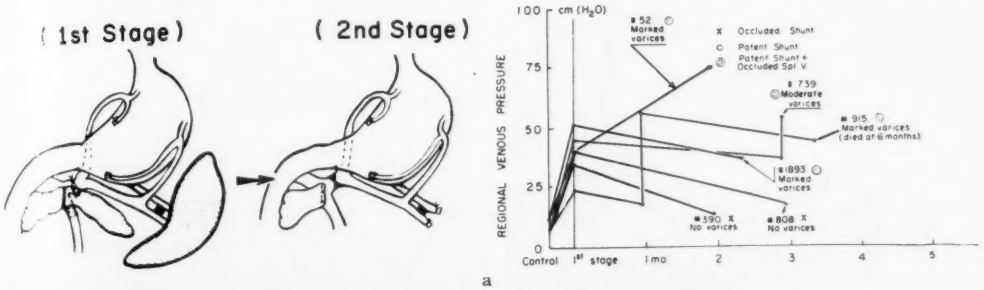


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FIG. 2. Group 2. This involved a procedure similar to that in group 1. However, a more extensive resection of potential collaterals was made, and in particular the tail of the pancreas was removed. a, Representative examples in this group are shown. Esophageal varices were consistently found in those animals with a patent shunt and an occluded splenic vein. In addition, these animals exhibited sustained elevations of pressure, in general, over 40 centimeters of citrate. b, A postmortem injection study on animal No. 915 referred to in a. There are extensive gastroesophageal varices flowing into the azygos vein. The final venous pressure measurement made at 3½ months was 47 centimeters of citrate. c, Histologic section of the esophagus in an animal of group 2 sacrificed at 2 months. Large submucosal varices may be seen. The pressure prior to sacrifice measured 48 centimeters of citrate.

occluded by organized thrombus. Both of these animals had lower pressures and less extensive varices. In the final animal, both vein and shunt had occluded. The pressure measured 20 centimeters and no varices were demonstrated.

Group 4. This experiment was designed to study the effect of the shunt alone. In essence, this procedure was identical to that used in groups 2 and 3. However, the splenic vein was not occluded. Five animals were long-term survivors in this group. Results

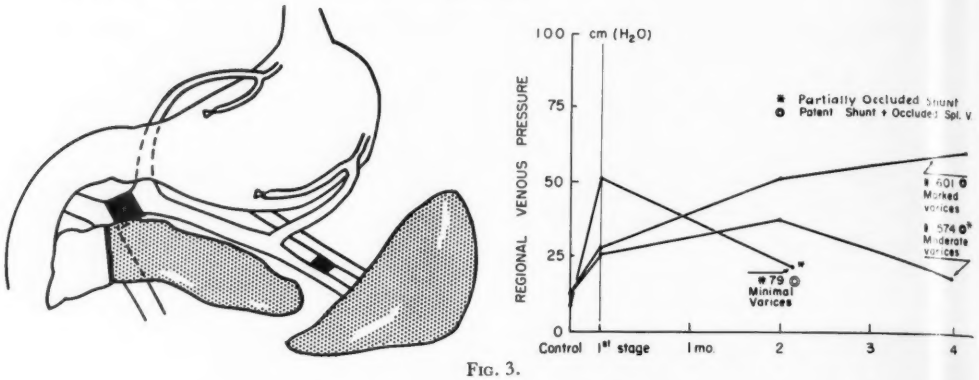

FIG. 3.

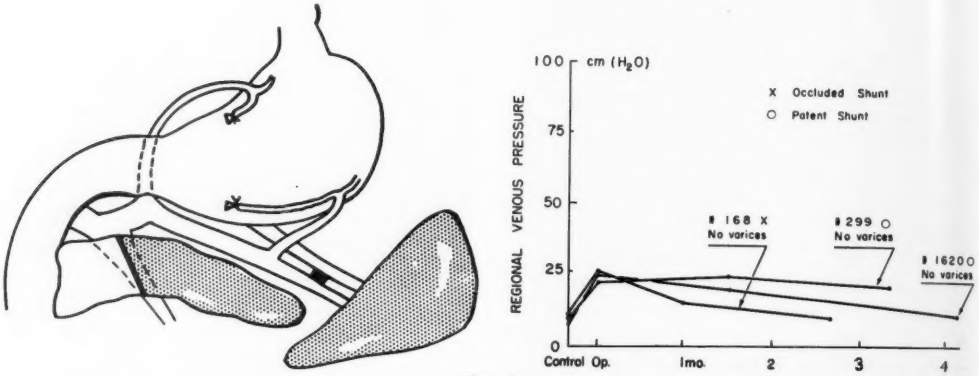

FIG. 4.

FIG. 3. Group 3 differed from group 2 only in that the procedure was performed in one stage. Gradual occlusion of the splenic vein was brought about by the application of a reactive cellophane band.

FIG. 4. Group 4, control. This procedure was the same as that in groups 2 and 3. The splenic vein, however, was not occluded. The venous pressure was only slightly elevated and varices failed to develop.

are shown in Figure 4. It will be seen that the pressures were slightly raised by this procedure but did not exceed 25 centimeters of citrate, and no varices were demonstrated.

Group 5. The purpose of this control group was to study the effect of venous occlusion and extensive removal of potential collateral pathways. An arteriovenous fistula was not made in dogs in this group. The spleen, the tail of pancreas, and the omentum were resected as in group 2 and the splenic vein was occluded with a silk ligature to produce varying initial levels of venous pressure above 30 centimeters of citrate, as shown in Figure 5. Five animals of this group, surviving 2 to 6 months, were available for study. It will be seen that esophagogastric communications were demonstrable in 2 of the 5 animals. These were of smaller size and did not approximate those seen in either group 2 or 3. Although sustained venous hypertension could not be produced by complete occlusion of the splenic vein and extensive removal of the extraesophageal collateral circulation, yet definite gastroesophageal communications were demonstrated in 1 animal up to 2 months and clearcut esophageal varices in another at 3½ months. In both animals, the initial venous pressure was extremely high and no

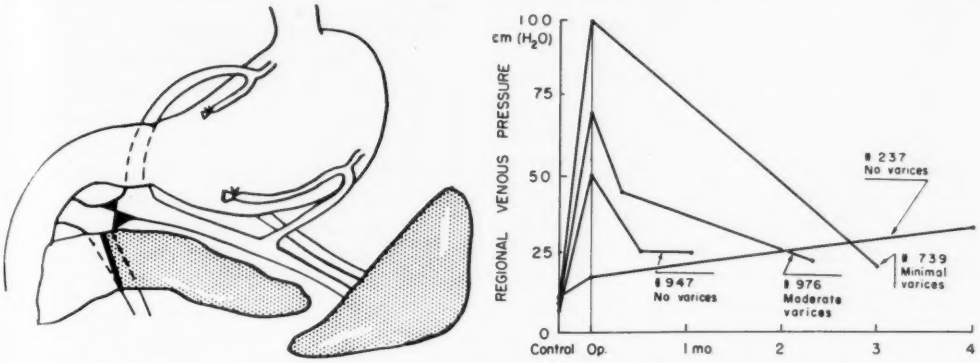

FIG. 5. Group 5. Venous occlusion control was similar to the procedure in groups 2 and 3 except that a shunt was not created. Representative animals are shown. The raised venous pressure was not sustained. Less extensive varices developed in some animals

route, other than that through the veins in and around the esophagus, was available.

The results obtained thus far indicated that definite esophageal varices and sustained venous hypertension developed regularly in animals surviving after splenic vein occlusion with a patent arteriovenous fistula. Extensive resection of extraesophageal collateral venous drainage was found to be necessary to channel the increased flow into the gastroesophageal venous plexuses. The role of the shunt appeared to be important both in sustaining venous pressure at raised levels over long periods and in magnifying the gastroesophageal communications which must develop after venous occlusion and removal of alternate collateral venous pathways.

Large shunt and progressive portal narrowing without removal of the collateral venous circulation. The foregoing studies suggested that the development of sustained venous hypertension and extensive varices was greatly influenced by the increased flow through the splenic arteriovenous fistula. To obtain a preparation in which the flow could be increased to such an extent that removal of the collateral venous drainage was unnecessary, the following experiments were carried out.

The external jugular vein was removed and anastomosed end-to-side to the portal vein above and to the aorta below in 12 dogs. After 3 to 4 weeks, a cellophane band was placed around the portal vein on the hepatic side of the shunt. The band was narrowed gradually until the portal venous pressure reached 40 centimeters of citrate. In control animals, the cellophane band was placed in the same manner but no shunt was made. In neither group was the spleen, omentum, or pancreas removed, nor were any of the retroperitoneal veins disturbed. Virtually complete occlusion of the portal vein developed in approximately 6 weeks. The results of this study are shown in Figure 6a, b, and c. In the 3 dogs with a patent shunt, the pressure before application of the constricting band measured 20 to 30 centimeters of citrate. At that time, enlarged veins were seen throughout the peritoneal cavity. At re-exploration, 1 month after application of the constricting portal band, the veins throughout the peritoneal cavity had become remarkably prominent. At this stage, the portal venous pressure in 2 dogs measured 40 and 48 centimeters of citrate, respectively, and the most extensive esophageal varices of the whole study were found in these animals. The shunt had partially occluded in the third dog. Pressure in this animal measured 23 centimeters of citrate, and no varices were found. Similarly, in 5 control dogs, in which the constricting band

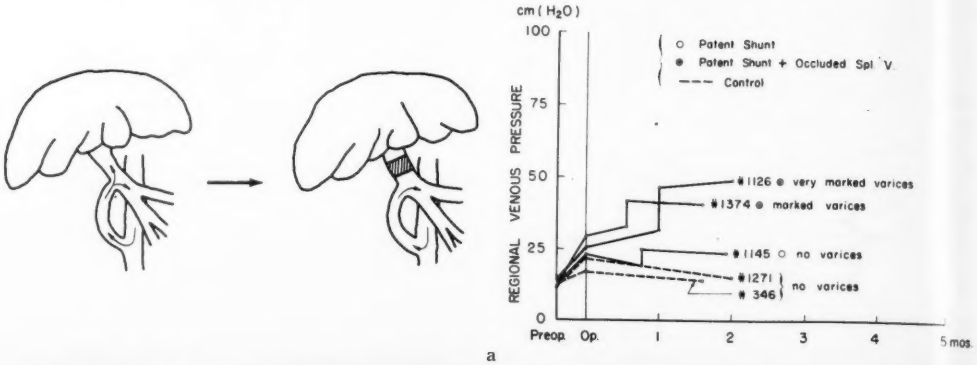

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FIG. 6. a, A shunt was created between the aorta and the main portal vein, followed by progressive occlusion by a cellophane band at second stage. In this group, sustained portal hypertension was associated with most rapid and marked development of esophageal varices. Two control animals are also shown. In these, the portal vein was occluded but the shunt was not made. Portal venous pressure remained low and no varices were noted. b, Portal venogram of dog No. 1126 during life shows extensive varices draining into azygos vein. c, Postmortem injection of everted esophagus of dog No. 1126 shows extensive esophageal varices and esophagitis.

had been placed but no shunt made, the pressures measured less than 20 centimeters of citrate and varices were absent. It is of some interest that the portal venous pressure in the group of animals with the aortoportal shunt failed to reach the levels recorded in groups 2 and 3, yet varices developed more extensively and more rapidly. This finding would appear to implicate the important role of increased flow as a cause of varices.

DISCUSSION

Previous attempts at producing esophageal varices have centered largely around the production of intrahepatic or extrahepatic portal venous obstruction. It now appears apparent that in the dog the extraesophageal portal systemic venous connections are sufficiently well developed to accept the normal splanchnic blood flow without the development of sustained portal hypertension and esophageal varices. However, when the capacity of the venous collaterals is strained by increased flow through an arteriovenous fistula, both a sustained increase in pressure and esophageal varices develop regularly. Moreover, at similar pressures, the extent of the varices appears to be related more closely to the volume flow through the splanchnic venous bed than to the level of pressure. It thus appears likely that increased portal venous flow may be equally as important as the obstructive factor in the pathogenesis of esophageal varices. The inconstant relationship between the level of portal venous pressure and the extent of esophageal varices is emphasized by Morton and Whelan. Low pressures recorded late in cirrhosis may simply reflect a widespread collateral venous response to a pressure rise occurring early in the course of the disease. Such a supposition would agree with the findings in the experimental study which show that significant varices failed to develop when the portal venous pressure was not sustained above 30 centimeters of citrate for at least 4 weeks.

During the course of these experiments, an operation was performed upon an 18 year old boy with extensive esophageal varices resulting from congenital arteriovenous fistulas between the splenic artery and vein. It is noteworthy that the azygous venous blood sample of this patient was highly saturated with oxygen. Varices have also been noted in association with hepatoportal fistulas. Although experiments such as those reported and rare clinical cases of naturally occurring fistulas offer gross pathways for increasing splanchnic venous blood flow, certain observations by others suggest that a more subtle expansion of existing arteriovenous communications in the splanchnic bed may produce a similar result. Taylor, Longmire, Womack and Peters have shown that the portal venous blood in cirrhotic patients may be highly saturated, and the finding of bright red bleeding is a common clinical experience in hemorrhage from esophageal varices. In addition, a recent article by Eiseman and his associates suggests that the lowering of portal venous pressure brought about by vasopressin results from temporary closure of myriads of small splanchnic arteriovenous shunts. Anatomic studies of the normal stomach and bowel by Barclay and Bentley have emphasized the magnitude of these shunts. Moreover, it is now becoming apparent that extensive generalized hemodynamic changes may occur in cirrhotic patients. Kowalski and Abelmann found an elevation of resting cardiac output, increased stroke volume, and low peripheral resistance in 7 of 22 cirrhotic patients. Moreover, Lunseth and his associates have demonstrated cardiac hypertrophy in 32 per cent of 37 patients studied at necropsy. The exceptional ability of these patients to form vascular communications is also shown by the anastomoses which develop between the portal and pulmonary veins and between the pulmonary artery and pulmonary veins in cirrhosis. Silverstein has recently shown a low arteriovenous oxygen difference in the peripheral veins of cirrhotic patients.

Taken in the aggregate, these experimental and clinical findings support the concept that an increased portal venous flow may contribute to the development and progression of esophageal varices.

SUMMARY

Various experiments designed to produce esophageal varices in the dog are described. Success was obtained when portal or splenic obstruction was associated with an increased flow into the portal system produced by an arteriovenous shunt. The possible role of

increased portal venous flow in the pathogenesis of esophageal varices is discussed in relation to both the experimental and clinical problem.

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ARTIFICIAL BLADDER FROM GASTRIC POUCH

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IN CASES in which it has become necessary to divert the urinary flow, methods developed have all had definite disadvantages as well as advantages. The disadvantages have outweighed the advantages in most instances in any of the methods attempted, and many patients so treated surgically have eventually succumbed to the results of the procedure.

When the ureters have been implanted into the colon, deleterious clinical changes have ensued, such as acidosis, hyperchloremia, azotemia, and hypokalemia; these may become fatal when renal failure occurs by ascending infection from the colon. Lloyd and Baumrucker have decried implantation of the "clean ureter into the dirty colon" and would rather employ skin ureterostomy with its own train of serious complications.

Rolnick finds skin ureterostomy and ureterosigmoidostomy unsatisfactory. Matern has stated that after ureterosigmoidostomy electrolyte imbalance was as inevitable as the pyelonephritis which in itself was a factor producing it. Ferris and Odell reported 112 patients of a series of 141 cases, or 79 per cent, in whom hyperchloremic acidosis developed due to intestinal absorption of chlorides from the urine. In his series, Lapides found urographic evidence of abnormalities and also electrolyte imbalance in 77 per cent of 22 cases of ureterosigmoidostomy with recurrent pyelonephritis. It was Lapides' opinion that the pyelonephritis was the primary cause of the electrolyte imbalance and that the absorption from the colon was a secondary cause.

Pool and Cook observed urographic changes as early as 6 months after ureterosigmoidostomy. Hypokalemia and acidosis associated with ureterosigmoidostomy has been described by Albright and associates as being due to tubular insufficiency without glomerular insufficiency and a decreased ability of the kidney to conserve potassium. Stamey (14) has concluded that patients with diversion of the urine to the colon, regardless of how much colon is used or if only one ureter is employed, may lose potassium because of an osmotic diuresis which occurs when chloride, sodium, and urea are absorbed in sufficient quantities from the bowel. In addition, secretion of potassium by the colon may contribute to the loss of this electrolyte; Stamey believes that pyelonephritis is not a major factor. When ureterosigmoidostomy is performed the resulting potassium depletion may be so severe that it causes respiratory paralysis which may simulate anterior poliomyelitis or Landry's ascending paralysis as reported by Straffon and Coppridge. Treatment with potassium chloride produced dramatic relief.

Stamey has defined the problem of electrolyte imbalance resulting from ureterosigmoidostomy as a serious one, since the hyperchloremia tends to cause acidosis whereas hypokalemia tends to cause alkalosis. If potassium deficiency is severe enough, the usual intravenous therapy with glucose, lactate, or sodium bicarbonate may cause sudden death. The physician, even in the face of a normal potassium level and dehydration, would hesitate to give potassium unless the urinary output was firmly established. Hypokalemia in itself may produce renal insufficiency. Stamey concludes that, unless there is a rapid and continuous run-off of urine in a short colon segment, the operation of ureterosigmoidostomy should probably be abandoned.

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Lloyd and Baumrucker view the presently used diversion techniques pessimistically. Some of the patients in their series never recovered from electrolyte imbalance and died with uremia; others, who might have recovered from electrolyte imbalance, suddenly collapsed, became stuporous, and died in uremic coma. In 10 of 14 autopsied cases, pyelonephritis was a major cause of death. There were few 5 year survivals, and the greatest mortality rate was in the first year, even in good risk patients. So strongly do they feel about their unsatisfactory results with ureterosigmoidostomy that they propose conservatism and palliative rather than radical treatment for carcinoma of the bladder, at least until a more satisfactory method of urinary diversion has been found.

Bricker has utilized an isolated ileal segment as a substitute urinary bladder. Of 28 patients, pyelonephritis has developed in 8 within 6 to 22 months. Seventy per cent of the 55 patients studied who had transplants were found to be normal or to have only minimal hydronephrosis. Stamey and Scott have reported favorably on this method as an improvement over ureterosigmoidostomy; however, they issued a note of warning concerning possible electrolyte disturbances. With use of an ileal loop, absorption from the isolated ileal segment continued. Pyrah and associates, quoted by DeWeerd, have shown that absorption of urea, sodium, chloride, and potassium occurs, although there is no differential absorption of sodium or chloride to possibly produce acidosis. Significant hypercalcemia, however, may develop especially in the presence of renal insufficiency. Couvelaire, also quoted by DeWeerd, has shown that in man the length of the ileal segment should be 25 centimeters or less to avoid electrolyte irregularities. Of all the reported methods using segments of the intestine, the method of Gilchrist and associates (5, 9) shows promise.

In the consideration of the problems inherent in transplantation of the ureters, it was believed that an isolated stomach pouch of the Heidenhain type would fill the criteria. It was proved in the dog (12), in which this method was used, and in some of the animals studied for more than 15 months, that:

1. The mucosa of a stomach pouch is practically nonabsorbing, obviating the changes in blood chemistry due to absorption of urine which occurs when bowel is used. There was no hyperchloremia, hyperchloremic acidosis, or azotemia.

2. There was no appreciable loss of electrolytes from the isolated gastric pouch and thus no hypochloremia or hypokalemia.

3. The gastric secretion of acid and lysozyme constitute a physiologic and bactericidal barrier which normally protects the small intestine against infection and which protects the kidneys against ascending infection. Normal pyelograms and the excretion of normal urine were seen in the dog, indicating normal renal function.

4. Stomach tissue beyond the needs of the animal was readily available for use as an artificial urinary bladder. After use of a portion of the stomach for a Heidenhain pouch or for an artificial urinary bladder, the remainder of the stomach eventually regained its original size and shape.

5. The length of ureter was more than adequate to reach the pouch easily. Only a proximal portion of the ureteral length was utilized for the anastomosis, thus minimizing the chance for constricting adhesions to form along its course.

6. Although no continent bladder was formed, it is believed that such a structure may be provided with an outlet valve.

7. In the dog, bilateral ureteral transplants into an isolated pouch were feasible, practical, and well tolerated, the animal living for 2 years in good health without electrolyte changes, azotemia, or ascending urinary infection.

8. Urine introduced into the pouch or into the stomach of the dog did not affect pouch secretion. The isolated vagotomized pouch responded to the gastric mechanism and to histamine injection.

9. No renal or ureteral damage was evident which might have been caused by acid regurgitation from the gastric pouch.

10. When hazards such as kinking of a ureter or stenosis of the ureterogastric anastomosis were avoided or corrected, the dogs appeared normal, and tests indicated normal kidney function.

Having observed the advantages of this method of urinary diversion in the dog and having developed the surgical technique (13), we performed our first operation upon a patient to produce an artificial urinary bladder from an isolated gastric pouch. In the follow-up it was determined that:

1. A gastric pouch could be utilized successfully as an artificial urinary bladder in a young woman with an inoperable cancer of the bladder.

2. After operation there was no evidence of kidney infection.

3. There was evidence of improvement in configuration and functional ability of the hydronephrotic kidneys.

4. Normal function of the remaining part of the stomach was demonstrated.

5. Without benefit of antibiotic or chemotherapeutic agents or urinary antiseptics, the urine returned to normal except for an asymptomatic culture of Aerobacter aerogenes, probably associated with the indwelling catheter.

6. When stimulated with histamine, the pouch secreted hydrochloric acid.

7. Repeated endoscopy revealed the gastric mucosa of the artificial bladder to be essentially normal and to have functioning ureteral orifices.

8. The area of the operation was not contiguous to the site of the carcinoma.

This first patient survived 18 months after operation and died of generalized carcinomatosis. Even terminally, there was no electrolyte imbalance or symptomatic urinary infection producing chills, fever, or impairment of urinary excretion.

Thus it was proved that in the human being an artificial urinary bladder made from a portion of the stomach was feasible.

In the postoperative study of the patient, it was believed that certain improvements in this operation would add to the comfort of the patient and to the safety and facility of the operation itself. These improvements were: (1) an operation that avoided the ultimate necessity for chronic catheterization of the artificial bladder; (2) the avoidance of the uphill drainage of the ureters from the renal pelvis to the artificial bladder. A vertical rather than a transverse artificial bladder would allow dependent drainage and a stoma at or below the level of the waistline. It would allow the application of a cemented Duff type bag to the lower abdominal wall. The vertical artificial bladder could be located in the vertical or vertical-oblique plane to meet a short ureter. The vertical pouch would lend itself to the forming of a valve at the stoma. These technical approaches were studied in fresh autopsy material, and the improved method was used in the second successful human case.

A white male, aged 77 years, was admitted to the hospital on 5 October 1958. Upon admission the patient was leaking urine and blood from the site of a suprapubic cystostomy. He was suffering from stress incontinence, small bladder capacity, and hematuria. He had been treated 4 years prior to admission with female sex hormones for obstructive prostatic hypertrophy without relief. In May 1956 a bladder tumor was discovered and removed by the suprapubic approach. In June 1956, a suprapubic prostatectomy was performed. In January 1958, a small contracted bladder was found with a capacity of 2 ounces, and the patient was advised to have a cystectomy and bladder substitute.

Physical examination on admission revealed a well developed, well nourished, obese, normotensive, elderly white male in no acute distress. His chest, lungs, and heart revealed no evidence of disease; the abdomen was obese and soft and showed midline surgical scars. There was a small midline, chronically suppurating opening with a slight but persistent leakage of urine on suprapubic pressure. There was no visceromegaly and no flank pain or tenderness. The external genitalia were normal. Rectal examination disclosed no evidence of disease. Temperature on admission was 99.6 degrees F. He was serologically negative for syphilis.

Preoperative laboratory studies, made on 6 October 1958 showed the following findings: leuco-

FIG. 1. Preoperative intravenous pyelogram showing normal kidney configuration on the right side and pyelectasis, caliectasis, and ureterectasis on the left side.

cytes 15,150; hemoglobin 14 grams; (87 per cent), hematocrit 42.5. A differential count showed stab cells 2 per cent; polymorphonuclears 86 per cent; basophils 1 per cent; lymphocytes 10 per cent; monocytes 1 per cent; and platelets adequate. The urine was cloudy, with a *p*H of 6.0, a specific gravity of 1.017, protein 2 plus, no sugar or acetone, no casts, many red and white blood cells, few epithelial cells, many triple phosphate crystals, numerous bacteria, many amorphous urates, occult blood, and no mucus. Serum urea nitrogen was 27 milligrams per 100 milliliters; serum creatinine 1.8 milligrams per 100 milliliters; serum chloride 102 milliequivalents; carbon dioxide combining power 22 milliequivalents; serum total protein 7.3 grams per 100 milliliters; albumin 4.1 grams per 100 milliliters; globulin 3.2 grams per 100 milliliters; albumin-globulin ratio 1:3. Thymol turbidity was 2.6 units, and cephalin cholesterol flocculation, serum acid, and alkaline phosphatase were all within normal limits.

Roentgenographic examination of the upper gastrointestinal tract disclosed a normal stomach and duodenum; This finding is important, since a portion of the normal stomach is used as the artificial urinary bladder. An intravenous pyelogram (Fig. 1) showed normal kidney structure and function on the right side and low urinary ureterectasis, pyelectasis, and caliectasis on the left side. Only the right half of the bladder filled. There was a large space-occupying lesion in the bladder. The impression was recurrent carcinoma of the urinary bladder with postresection contracture and fistula formation with obstructive uropathy of the left ureter.

On 7 October 1958 an operation was performed wherein an artificial urinary bladder was formed from a segment of the stomach into which both ureters were implanted. With the patient under general anesthesia a right paramedian incision was made from the xiphoid process to the suprapubic area, and the peritoneal cavity was opened. The liver was enlarged and the omentum was adherent in the pelvis as a result of the previous operations. The omental adhesions were freed and the omentum was freed from its natural attachments to the transverse colon, from the splenic flexure, and from the spleen. The lesser omental space was entered through the gastrocolic ligament. A segment of the greater curvature of the stomach was taken to be used as the artificial urinary bladder (Fig. 2). This portion of the stomach consisted of a large part of the fundus adjacent to the splenic vasa brevia which were divided between clamps extending to the proximal portion of the gastric antrum. The left gastroepiploic artery was divided and tied. The continuity of the right gastroepiploic artery was carefully preserved.

The segment of stomach separated from the residual stomach with its right gastroepiploic artery intact was then wrapped in a moist laparotomy pack. The bleeding vessels on the cut edges were ligated.

The left ureter was identified lateral to the sigmoid flexure by incising the posterior parietal peritoneum. This segment of ureter was then freed by sharp and blunt dissection proximal to the palpable bladder mass. At this distal point the left ureter was divided and the distal end was tied with No. 00 black silk. The proximal portion of the left ureter was freed and brought into the free peritoneal cavity at the level of the left kidney pelvis by incising the posterior parietal peritoneum medial to the descending colon in juxtaposition to the pouch.

The ascending colon was mobilized medially and the right ureter was mobilized and transected at its junction with the bladder. The distal transected end was tied with No. 00 black silk. The proximal end was brought through the ascending mesocolon and the omentum to the gastric pouch which, vertically placed, now lay in the medial right half of the peritoneal cavity.

At a point where the right ureter was brought to the gastric pouch without tension, an area of a gastric rugal fold was seized with a hemostat and 0.5 centimeter of mucosa was excised. In a technique previously described (12) a right end-to-side ureterogastrocystostomy was performed.

The mobilized left ureter was brought into position with the gastric pouch by bringing it through the proximal mesojejunum, and an end-to-side left ureterogastrocystostomy was performed.

The catheters placed into the ureters as previously described (12) were allowed to assume positions without tension and were held in place and the pouch closed about them with a mucosal layer of No. 00 chromic gastrointestinal catgut and seromuscular approximating interrupted sutures of No. 00 black silk. The distal end of the pouch was left open to act as the stoma.

The abdomen was closed in layers without tension around the pouch, much of which was in transit

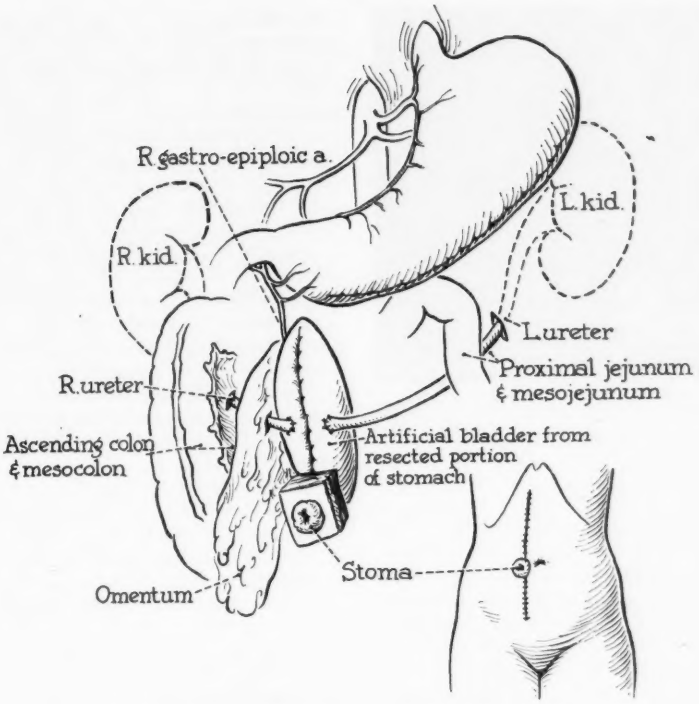

FIG. 2. Illustration of the operation described in the text.

through the anterior abdominal wall in this obese patient. The pouch was fixed by sutures at the levels of peritoneum and fascia. A circular portion of skin and subcutaneous fat in the right border of the incision was excised, allowing room for the stoma. Penrose drains were led to the fascia. The gastric mucosa of the pouch was sutured to the skin. The separate ureteral catheters leading through the stoma were each led to a drain bottle, and the wound was dressed.

Postoperatively the patient did well. The urine from each catheter was analyzed from the date of surgery, 7 October, to 13 October, when the patient removed the ureteral splinting catheters himself. The *p*H of the urine ranged from 5 to 8 for the right ureter which was the one undamaged by obstruction. The *p*H of the urine ranged from 7.5 to 8.0 from the left ureter which was damaged by obstructive uropathy. Occult blood disappeared from both right and left ureters on 12 October, 5 days postoperatively. Gross blood disappeared from urine from the right kidney 1 day sooner than from urine from the left kidney. The specific gravity of urine from both right and left kidneys was essentially the same, as was the proteinuria. The white blood cells in the urine were essentially the same for right and left ureteral samples. Other findings were not remarkable.

Pouch urine, a mixture of urine from both kidneys and gastric pouch secretion was collected from 14 October, 1 week postoperatively, to 30 October 1958. The *p*H of this urine ranged from 6.5 to 7.5 and specific gravity from 1.009 to 1.016. A faint trace of protein persisted but may have been derived from gastric secretion. Casts diminished progressively as did the red blood cells and white blood cells. There were no bacteria in the last sample collected. Pathologic elements diminished progressively except triple phosphate crystals. Although time and progressive healing may have been a factor, a more rapid and definite return to normal was noted after the ureteral splinting catheters had been removed.

The patient preoperatively had a blood urea nitrogen of 27 milligrams per cent (normal, 10 to 20). This rose to a postoperative level of 35 milligrams per cent for 2 days and then declined. Twenty-three days postoperatively the blood urea nitrogen was 19 milligrams per cent.

The serum creatinine preoperatively was 1.8 milligrams per cent (normal, 1 to 2). This level rose 2 milligrams per cent 1 day after operation, then dropped to 1.4 milligrams per cent on 30 October, 23 days postoperatively.

The rise in these two factors in the postoperative

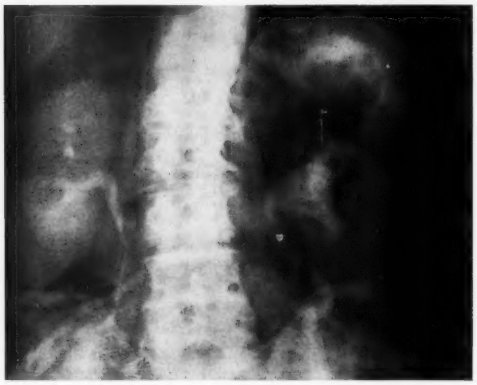

FIG. 3. Intravenous pyelogram 24 days after operation shows improved renal configuration and function on the left as indicated by dye excretion. Also shown is the course of the ureters to the artificial urinary bladder.

period was probably due to stress, anesthesia, and possibly fluid or electrolyte imbalance.

Serum chloride levels remained essentially normal throughout the observation period, ranging from the preoperative level of 102 milliequivalents (normal 98 to 106) to a low of 91 milliequivalents on the fourth postoperative day to 99 milliequivalents 23 days postoperatively. At no time was there hyperchloremia. The low level of 91 milliequivalents was probably due to inadequate postoperative chloride administration. The carbon dioxide capacity (25 to 29 milliequivalents normal) ranged from a 22 milliequivalent preoperative level to 31 milliequivalents 11 days postoperatively, and then to a normal 28 milliequivalents 23 days postoperatively. Serum sodium and serum potassium remained essentially within normal limits. Serum sodium rose to 159 milliequivalents 1 week postoperatively but returned quickly to normal. Mild hypopotassemia, 3.8 milliequivalents, occurred on one occasion 6 days postoperatively and returned to normal by the next day and remained so. Total protein, albumin, globulin, and the albumin-globulin ratio as well as thymol turbidity, cephalin flocculation, and serum phosphatase, both acid and alkaline, were all within normal limits on the patient's admission to the hospital, 6 October 1958. On the eleventh postoperative day serum albumin and albumin-globulin ratio had dropped slightly. This was not serious and it was believed that improvement in protein nutrition would correct this slight defect. A blood count 11 days postoperatively showed no evidence of anemia.

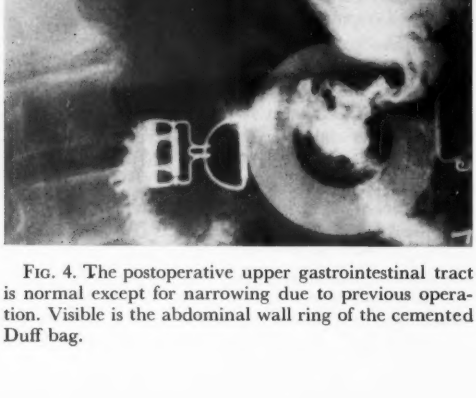

FIG. 4. The postoperative upper gastrointestinal tract is normal except for narrowing due to previous operation. Visible is the abdominal wall ring of the cemented Duff bag.

On the fourth day after the operation constant gastric suction was no longer necessary, and after the fifth day the patient took sufficient liquids orally to satisfy his needs.

Postoperative temperatures never exceeded 100.2 degrees F. and became normal for the week prior to discharge. The postoperative pulse rate was 100 per minute the first postoperative day and ranged between 80 and 100 generally, except for 3 days when, on 20 October, 1 day after a separation of the skin incision, it was 110 per minute and the temperature was 100.2 degrees F. The pulse rate was 60 per minute on discharge. Cardiac decompensation was never present. Respirations followed the temperature curve and were 18 per minute on discharge. At no time was there any pulmonary edema. Bowel movements occurred normally, and postoperative distention was minimal. Peristaltic sounds, never absent, became normal in the early postoperative period.

Skin stitches were removed on 17 October and on this day the skin and subcutaneous layers separated after a cough. The skin was resutured with the patient in his bed, using local anesthesia. These stitches were removed on 30 October and there were no further complications.

On 31 October, 24 days after operation, an intravenous pyelogram (Fig. 3) showed improved configuration and function of the left kidney as indicated by dye excretion. Also shown is the course of the ureters to the artificial urinary bladder.

At clinical follow-up, on 4 February 1959, 4 months after operation, the incision was well healed except for two small fistulas at the site of the old suprapubic cystotomy. Blood electrolytes, blood nitrogen, and creatinine were within normal limits. Three urinalyses without stimulation of gastric secretion showed no occult blood.

A gastric analysis was performed after histamine administration Anticipated response was normal and produced a *p*H of 8.0 in samples of pouch urine collected simultaneously.

Blood chemistry studies were made on 5 February and 10 February, approximately 4 months postopera-

tively. All values were within normal limits. An electrocardiogram taken 5 February was normal. Follow-up roentgen ray studies during this hospital stay included an upper gastrointestinal series, a chest roentgenogram, and an intravenous pyelogram and were reported as follows:

Examination of the upper gastrointestinal tract (Fig. 4) after a barium meal revealed no evidence of organic lesions in the esophagus. The antrum of the stomach appeared to be narrowed, apparently the result of previous operation performed at this site. The stomach showed good peristalsis and normal emptying. The content of the stomach passed through the antrum without any difficulty. The duodenal bulb was not deformed or distorted. The duodenal loop appeared entirely normal. On several films metallic parts of the rubber bag pasted to the abdominal wall are superimposed on the gastric antrum. Visible loops of jejunum appeared entirely normal. No abnormalities were demonstrated in the upper gastrointestinal tract except for narrowing of the antrum due to previous operation.

An intravenous pyelogram (Fig. 5) revealed a considerable improvement of the hydronephrosis on the left side in comparison to previous examinations performed before construction of an artificial bladder; compared with the right kidney, however, there is still a slight degree of caliectasis. On a film of the abdomen (Fig. 6), which was taken after the instillation of dye into the artificial bladder on 11 February, 4 months after operation, there is quite considerable caliectasis, pyelectasis, and ureterectasis which may be explained partly on the basis of backflow under pressure, since the capacity of the new bladder is rather limited. Shown also is the filled artificial bladder, a catheter leading into it, and its relation to the barium filled colon and lumbar vertebrae. There was no reflux into the right urinary system. However, in view of the fact that the right kidney was entirely normal on these films taken during the intravenous pyelography, it may be assumed that the ureter on this side is functioning normally, too. Unfortunately, some of the details are obscured by barium filled loops of large bowel.

The impression is that retrograde and excretory urograms reveal a considerable improvement of the hydronephrosis of the left kidney and normal conditions on the right side. The artificial bladder is apparently functioning well, as far as can be determined roentgenologically.

On 11 February 1959 a No. 24 panendoscope passed through the stoma of the gastric pouch without obstruction. A thorough examination of the pouch showed: (1) longitudinal and oblique folds of mucosa; (2) normal appearing mucosa, pinkish in color; (3) no areas of induration and no erosions; (4) one ureteral orifice about 2 inches from the stoma; (5) the size of the opening to be 2 to 3 millimeters; and that (6) the orifice opens with every jet of urine, then

FIG. 5. Intravenous pyelogram 4 months postoperatively reveals improvement of hydronephrosis on the left with still a slight degree of caliectasis.

closes. A No. 5 ureteral catheter was passed up through the orifice without obstruction.

Indigo carmine was injected intravenously; after 5 minutes the dye showed in the drainage from one ureteral catheter; culture of urine from this catheter yielded proteus sensitive in vitro to neomycin and mandelamine. The other orifice could not be found for catheterization.

A urethral catheter and bag inflated to 15 milliliters was left inside the gastric pouch; 50 milliliters of urograffin was gently injected while traction was applied to the catheter in order that the bag would seal off (Fig. 6). The cystogram was reported to show reflux of retrograde dye into the left renal pelvis probably precluded by the ureterectasis preoperatively on the left. There was no reflux on the right undilated side. Previous ureterectasis may thus be a

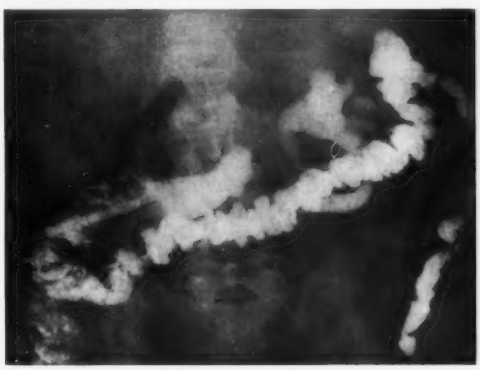

FIG. 6. Retrograde instillation of dye into the artificial bladder shows artificial bladder with reflux of dye into the left ureter and kidney, caliectasis, pyelectasis, and ureterectasis due to back flow under pressure. Also shown is the barium filled colon.

deterrent to attempts at making a continent urinary bladder, for fear of reflux, and may be an indication for early preureterectatic operation in cases in which a continent urinary bladder is contemplated.

SUMMARY AND CONCLUSIONS

1. A gastric pouch has been utilized as an artificial urinary bladder in an elderly man with cancer of the bladder, the author's second successful human case.

2. Four months after operation, without the use of chemotherapeutic or antibiotic drugs, there was no evidence of serious urinary infection.

3. There has been evidence of improvement in configuration as well as in functional ability of the severely impaired left kidney 4 months after operation.

4. Normal function of the patient's stomach has been demonstrated.

5. After operation the urine has returned to normal except for an asymptomatic culture of a proteus species.

6. Cystoscopy revealed the mucosa of the artificial bladder to be essentially normal with a functioning ureteral stoma.

7. Since the early postoperative period and as long as 4 months after operation, blood chemistry values are normal and the patient is not uremic.

8. The patient is comfortable and dry with the method used.

9. A continent artificial urinary bladder, using a gastric pouch, may be feasible if ureteral reflux can be prevented by early preureterectatic surgery, by the use of one of several possible techniques, and by the utilization of more gastric tissue as an artificial bladder.

10. A moderate lowering of urinary *p*H postprandially and after histamine stimulation suggests that the gastric mucosa of the artificial urinary bladder secretes hydrochloric acid. Both the gastrin mechanisms and histamine stimulation, demonstrated experimentally in the dog, were present also in the human patient.

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PREOPERATIVE EVALUATION OF THE CHRONICALLY ILL SURGICAL PATIENT BY TILT TABLE AND ADRENAL RESPONSES CORRELATED WITH BLOOD VOLUMES

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THE PROBLEM of hypotension in the chronically ill patient during induction of anesthesia or during an operative procedure has been observed with surprising frequency and can present a distressing or even fatal complication. The basic cause of this problem is not always apparent, though in the absence of heart failure or vasodilating drugs this phenomenon is most often due to a diminished circulating blood volume which may be present in spite of a normal hematocrit. Several workers have demonstrated diminished blood volumes in chronically ill patients with no significant change in the hematocrit. In recent years, with the introduction of adrenal steroid therapy, resultant adrenal insufficiency, often latent in nature, has been reported as an occasional cause of operative hypotension.

Tilt table testing similar to that employed by Brigden, Howarth, and Sharpey-Schafer and by Green and Metheny was chosen as a potentially simple method of detecting those patients more susceptible to operative hypotension. It was postulated that the tilt table results might correlate well with diminished blood volumes and in particular might indicate those patients with deficient postural reflex adjustments. It has been suspected that inadequate reflex mechanisms may develop in patients with long-standing disease processes and limited activity.

METHODS AND MATERIAL

The 77 patients in this study, nearly all of whom were being evaluated for surgery for chronic pulmonary tuberculosis, were seen at the Mississippi State Sanatorium. Their ages ranged from 14 to 73 years. A standard operating table was employed for the tilting. A wooden support was placed between the legs as a saddle, so that there would be no muscle exertion during the actual tilting. After initial recordings of the blood pressure, pulse, and respiration had been made in the supine position, the patient was placed in a 60 degree tilt with the head up. The vital signs were then recorded at 1 minute intervals for 3 minutes. The patient was then replaced in the supine position and another recording was made at the end of 2 minutes. Pneumatic tourniquets placed around the upper portion of the thighs were then inflated slightly higher than the diastolic pressure and maintained at this level while the patient was elevated for another 3 minutes. During this time blood pressure and pulse recordings were again made at 1 minute intervals for 3 minutes.

Stroke volumes and total cardiac output were calculated from the blood pressure and pulse determinations, according to the formula of Starr:

Stroke volume (ml.) = 100 − 0.6 age in years − 0.6 diastolic pressure + 0.5 pulse pressure
Cardiac output (ml.) = stroke volume × pulse rate.

Also, using this figure as a basis, the total peripheral resistance was calculated by the standard formula:

Total peripheral resistance (units) = diastolic pressure + ⅓ pulse pressure ÷ cardiac output per second

Although the results are plotted as units, these may be converted to absolute units by multiplying by 1,332 dynes^{-5}. According

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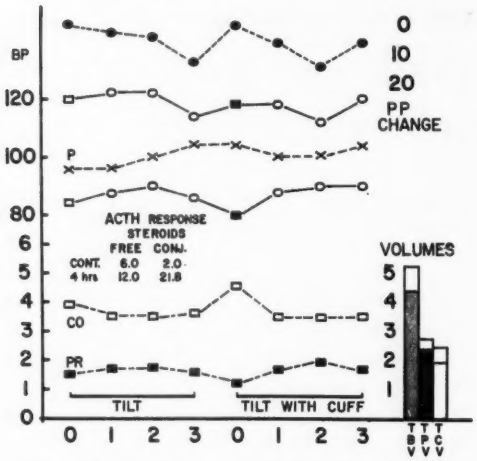

FIG. 1. Normal response to tilt test. There is a calculated blood volume deficit of 12 per cent with the hematocrit of 48. Note the maximal fall in pulse pressure of 14 points, the fall of the systolic pressure, the slight rise of the diastolic pressure, and the mild acceleration of the pulse rate. As anticipated, the cardiac output falls and the total peripheral resistance increases during the passive elevation with and without inflation of the cuffs. The adrenal response to ACTH stimulation is within normal limits. At the first attempt, this patient was so apprehensive that hypotension and extreme tachycardia developed even before the anesthetic was started. The second attempt proceeded uneventfully.

to the work of Starr and Assali and his associates (14), cardiac output as calculated from the blood pressure determinations gives a value fairly close to that obtained by the direct Fick measurements and not too unlike that obtained from Evans blue dye, nitrous oxide, or acetylene measurements. In particular, the directional change and the percentage change of the cardiac output calculated by this formula were found to be extremely reliable and to correlate quite well with other methods of determining cardiac output.

Blood volumes were measured by the Evans blue dye method (T-1824), using a Beckman spectrophotometer. Height-weight tables (surface area) were utilized for estimating "normal" blood volumes for each patient.

In addition, adrenal function studies were obtained in all patients exhibiting a positive tilt test or who had shown operative hypotension in spite of normal blood volumes. Adrenal function was measured by administering 40 units of ACTH intravenously over a 4 hour period with control and 4 hour determinations of the free and conjugated 17-21 hydroxycorticosteroids, according to the methods of Nelson and Samuels and of Bongiovanni. Also, absolute eosinophil counts were made at the beginning and at the end of the 4 hour period.

RESULTS

In this group, blood volumes were uniformly low. In 47.6 per cent of the patients studied the blood volume was found decreased to a greater than 15 per cent deficit in spite of hematocrit readings well within the normal range—frequently above 40 or even 45. This was true even though most of these patients had been under treatment for at least several months with adequate nutrition, and most were at or above their usual weight. None was cachectic or emaciated as from advanced carcinomas. Deficits greater than 20 per cent of their estimated blood volume were noted in 32.5 per cent of the patients, and 20 per cent had deficits greater than 25 per cent.

The usual response to 60 degree vertical tilting is characterized by a slight rise in diastolic pressure and a fall in systolic pressure which results in narrowing of the pulse pressure. Normally, there was only a slight increase in the pulse rate and little or no change in the respiratory rate (Fig. 1). From formula calculations it can be seen that cardiac output diminishes and peripheral resistance is increased.

A positive response to tilting was characterized by a more significant fall in the systolic blood pressure and the usual rise in the diastolic pressure. This caused a narrowing of the pulse pressure to 20 millimeters of mercury or less. A positive response to tilting is illustrated in Figure 2. A fall in the pulse pressure of 20 millimeters of mercury or by 50 per cent of the control pulse pressure correlated best with episodes of operative hypotension or measured defi-

cits of circulating blood volume greater than 20 per cent in magnitude. Of 23 patients with abnormal responses in this series, 18 patients had a blood volume deficit of 20 per cent or more. Most patients appeared able to compensate for anything less than a 20 per cent blood volume deficit. Eight of these patients had repeat tilt tests after restoration of the blood volume to normal, and all 8 then showed a normal response to the postural stress (Fig. 3).

Of the 5 patients with normal blood volumes and an abnormal tilt table test, 2 had very extensive, long-standing disease. One of these had, in addition, marked adrenal insufficiency. Two others were more than 70 years of age, 1 having an inoperable bronchogenic carcinoma and the other a large thoracic aortic aneurysm with pleural effusion (Fig. 4). The last patient in this group was a young woman with only a 10 per cent blood volume deficit who previously had had a left pneumonectomy, which appears to render the patient more susceptible to postural stress. As blood volume studies have shown a 15 per cent variation in the "normal," a 10 per cent blood volume "deficit" may actually be a much greater deficit than calculated.

On the other hand, there were 10 patients with a normal tilt test who were subsequently found to have a blood volume deficit of 20 per cent or more. Yet only 1 of these had a blood volume deficit greater than 25 per cent. It appears that some individuals are able to compensate by increasing the pulse rate by more than 20 points, or to a rate of over 100 per minute. Four of these patients subsequently demonstrated marked hypotension after induction of anesthesia, necessitating cancellation of the intended operative procedure. However, 3 of these 4 successfully underwent operations later after whole blood transfusions, and the fourth patient refused surgery.

In the remaining 53 instances the tilt tests were normal, and the blood volume deficits in these patients were less than 20 per cent in each instance.

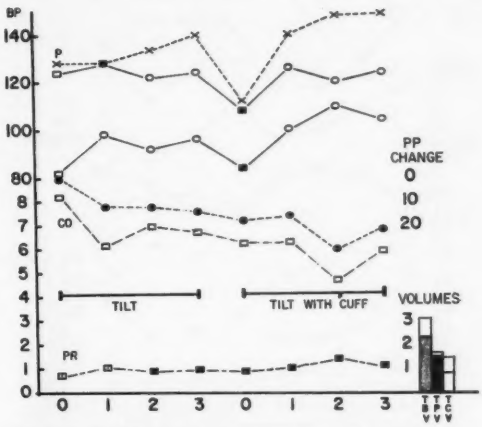

FIG. 2. Positive tilt test in patient with more severe blood volume deficit of 25 per cent and cell deficit of 45 per cent with the hematocrit of 36. Note the typical high cardiac output and diminished resistance which more than doubled under the test conditions. Many patients were able to compensate fully by a marked increase in cardiac rate, which occurred here, but less effectively, as the pulse pressure fell 35 points.

ADRENAL FUNCTION STUDIES

Adrenal function tests were performed in those patients in whom adrenal insufficiency might be suspected for any reason, such as an abnormal tilt test in the presence of a normal blood volume or operative hypotension with no obvious cause. Seventeen patients had ACTH stimulation studies, and 6 were found to have marked adrenal insufficiency. Three of the patients had a history of previous steroid therapy which is thought to account for the poor adrenal response (Fig. 5). Yet, the additional 3 patients, with no clinical evidence of Addison's disease or history of steroid therapy, had latent adrenocortical hypofunction as measured by the ACTH stimulation test. Likewise, all 3 had shown marked hypotension at surgery, in spite of normal blood volumes and normal tilt tests. They subsequently underwent uneventful operative procedures after adequate adrenal steroid therapy had been instituted. Two patients on further evaluation were found to have a positive Robinson-Kepler-Power water test for adrenal insufficiency.

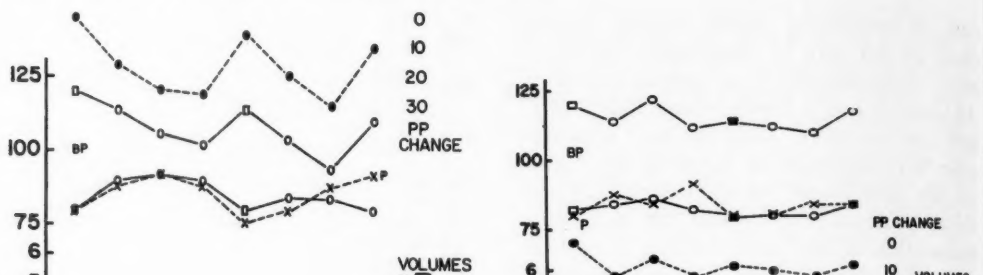

FIG. 3. a, Abnormal tilt response. Calculated blood volume deficit of 21 per cent in spite of normal hematocrit. Note the more marked alteration in blood pressure with a 30 point fall in the pulse pressure. b, Normal tilt test after a 500 milliliter blood transfusion. This patient had adrenal insufficiency as measured by both ACTH and the Robinson-Kepler-Power water test. The first operative attempt with hypovolemia resulted in hypotension. The second attempt, after correction of the blood volume, gave the same result. The third attempt, with hydrocortisone support, was uneventful.

AGE

In analyzing our data for any possible differences due to age, we found no difference in the response of those patients less than 40 years old and those between the ages of 40 and 60 years. Only 4 patients more than 60 years of age were tested in this series and all showed an increase in pulse rate about double that of the younger patients. Two of the 4 older patients had an abnormal tilt test with a marked fall in pulse pressure in spite of measured normal blood volumes. These 2 patients likewise showed operative hypotension in spite of normal blood volumes and normal adrenal responses (Table I).

Changes in pulse rate likewise did not correlate with the degree of anemia present. This is in contrast to the work of Brannon and coworkers who found a much greater increase in pulse rate in those patients who had chronic anemia, though we did not make a study of the extremes of anemia that they did.

TABLE I.—NORMOVOLEMIA AND NORMAL ADRENAL RESPONSE

Age, yrs.	*Pulse*	*Abnormal tilt test*	*Operative hypotension*
15–40	+10	2	1/31
40–60	+ 9.6	0	0/16
60+	+21	2	2/4

DISCUSSION

In the absence of some obvious cause such as heart failure, pregnancy, mitral stenosis, or vasodilating drugs, operative hypotension is most often due to diminished circulating blood volume. A shift in position from lying to standing is thought by Sjostrand to shift approximately 650 milliliters of blood into the lower extremities, most of this being shifted from the heart and lungs. In addition, Ebert and Stead demonstrated that tourniquets on the legs would trap approximately 700 milliliters of blood. Thus, the use of pneumatic tourniquets on the thighs would accentuate any blood volume deficit, and, combined with tilting, would be comparable to a massive hemorrhage averaging 10 to 15 milliliters per kilogram. Green and Metheny found a syncopal reaction almost

uniformly if acute bleeding exceeded 14 cubic centimeters per kilogram when a 75 degree tilt position was maintained up to 3 minutes. Longer periods of tilting, atropine, or lesser degrees of hemorrhage can induce vasovagal syncope. Using only a 3 minute period of 60 degree tilt, we did not find a single instance of syncope during our series. After a period of 24 to 72 hours of adjustment, the syncopal responses of Green and Metheny did not recur, as compensatory blood volume adjustments had been made.

Similarly, the work of Weissler and his associates has demonstrated that the syncopal response can be prevented by the antigravity suit, by negative pressure breathing, or by the administration of serum albumin or electrolyte solution just prior to tilting. These latter measures increase the circulating blood volume and thereby tend to reduce the importance of blood pooled in the lower extremities.

Within the past few years, adrenal insufficiency has been an occasionally reported cause of operative hypotension. This seemingly reflects the increased use of adrenal steroid drugs. During this period of study 13 patients showed episodes of operative hypotension. Six were associated with marked hypovolemia and 3 had hypovolemia plus adrenal insufficiency. One patient had adrenal insufficiency with a normal blood volume. Two patients were more than 70 years of age and the operations were also complicated by errors in anesthetic technique. One additional patient had a mild syncopal response, presumably due to his extreme apprehension, necessitating cancellation of his operative procedure. At the second attempt, however, given more adequate premedication, this patient did well. This latter emotional factor has been extensively studied by Stead and associates and Engel and Romano who find it, alone, to precipitate syncope on the tilt table.

The difference in response to tilting in the aged has been reported as slight but definite. In the aged, both the systolic and diastolic pressures usually fall, whereas in

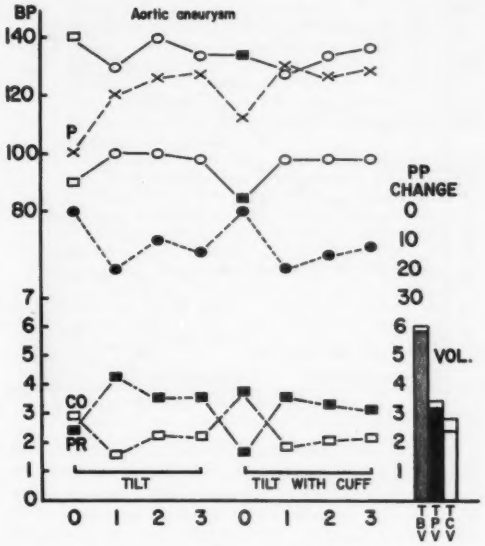

FIG. 4. Abnormal tilt response in the presence of normal hematocrit and blood volume. The patient's age and aortic aneurysm and pleural effusion probably played a role. The initially low cardiac output and high peripheral resistance showed marked inverse changes on tilting. Again there is an attempt toward compensation by marked elevation of the pulse rate. This patient experienced marked hypotension on induction of anesthesia, requiring cancellation of the operation.

the younger patients the diastolic pressure usually rises slightly. In addition, the pulse rate was found to accelerate less in the older group. This finding has been confirmed by the work of Norris and associates who also found a greater increase in the pulse rate and a greater elevation of the diastolic pressure in the younger group. In contrast, our elderly patients, all 70 or more years old, showed a marked increase in the pulse rate. However, no definite conclusion can be drawn, because there were only 4 patients in this particular group.

Part of the response to tilting, such as cardiac acceleration and increased peripheral resistance, is due to an immediate outpouring of norepinephrine, demonstrable in plasma levels more than double the control values. This fact may explain the instantaneous adjustment necessary to maintain relatively normal hemodynamics after as-

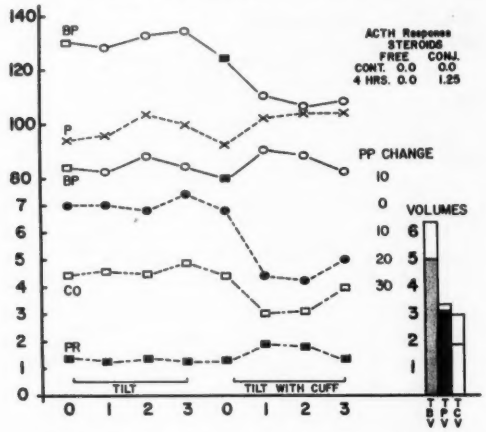

FIG. 5. Positive tilt test with blood volume deficit of 22 per cent and hematocrit of 39. Note the normal response to tilting without cuffs but marked drop in pulse pressure on inflation of the cuffs. There was almost no demonstrable adrenal function, presumably due to prolonged cortisone therapy for arthritis. The operative course was completely smooth after administration of 1,500 milliliters of blood and hydrocortisone support.

sumption of the tilted posture, and certainly this mechanism must be most important for the prolonged adjustment as more and more fluid pools in the lower extremities. Interestingly, Hickler and associates found that patients with essential hypertension have a normal cardiovascular response on tilting but do not show the expected increase in circulating norepinephrine. If, as is postulated by Hardy and coworkers, norepinephrine is secreted primarily from peripheral neural ganglia rather than from the adrenals, the tilt response of adrenal deficient patients would be anticipated to be normal, as was found in the present studies.

The adrenal function studies uncovered adrenal hypofunction in 6 patients. Although 3 of these patients had previous steroid therapy, the remaining 3 apparently represented true latent adrenal hypofunction. Two of the latter had additional evidence of adrenal hypofunction by the Robinson-Kepler-Power water test. These findings would indicate a higher incidence of adrenal hypofunction in chronically ill tuberculous patients than is generally realized. Thus, the need for making more complete investigative studies in the evaluation of chronically ill patients has become quite apparent.

It is significant that there was only 1 death related to the 89 operative procedures on 68 patients of this study group. This single death occurred in a colored female with extensive bilateral disease who succumbed from a pulmonary embolus on the third day after a pneumonectomy.

It was thought that this group with prolonged illness and enforced inactivity would demonstrate inadequate reflex adjustments to rapid and fairly extreme shifts in posture. Our findings, however, were related primarily to changes in blood volume, without any particular relationship to abnormal reflex mechanisms. Only 1 of this group of patients had an abnormal tilt test without other adequate explanation, such as a low blood volume or extreme age.

SUMMARY

Eighty-six tilt table tests have been performed on 77 chronically ill patients. Of 23 abnormal responses, 18 occurred in patients with significant blood volume deficits. Adrenocortical hypofunction was observed in 6 patients. Three of these patients had no previous steroid therapy or clinical evidences of adrenal hypofunction, representing a high incidence of latent adrenal insufficiency.

Tilt table testing, although a crude measure, is able to detect blood volume deficits above 20 per cent fairly consistently and almost uniformly above 25 per cent. The tests correlate even better with the operative hypotensive response due to hypovolemia. The tilt table test as used here does not detect inadequate reflex mechanisms, if such do exist, or the presence of adrenal insufficiency.

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STABILITY AND QUALITY OF PLASTIC TRANSFUSION EQUIPMENT

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INCREASING APPRECIATION by physicians of the need for blood component therapy, the ease of processing blood in a totally closed plastic system, the ready maintenance of identification of the sampling aliquots, and the ability to separate and infuse the components safely at rates indicated by the clinical situation have achieved broad acceptance for the comparatively new transfusion technique based upon the unique properties of plastic equipment. Despite the mounting satisfactory clinical experience with blood processed in plastic, questions persist concerning the possible toxicity of the plastic, its uniformity, and deterioration during storage. A review of data which have been accumulated during a 4 year period demonstrates the uniformity of the biologic interface of successive lots of plastic as well as its stability to aging.

Analysis of the data yields quantitative evidence on the following characteristics of plastic equipment: (1) the degree of conformance of the acid citrate dextrose (ACD) solution contained in the standard steam sterilized collection packs with the requirements of the *Pharmacopoeia of the United States;* (2) the immediate postinfusion survival of red cells of blood collected in the standard pack after storage for 21 days at 4±1 degree C.; (3) the effect of long term storage up to 4 years on packaged packs at warehouse temperature on the physical and biologic characteristics of the plastic material.

From the Departments of Surgery and Medicine of the Peter Bent Brigham Hospital, Boston, Massachusetts, and the Quality Control Laboratory of Fenwal Laboratories, Inc., Framingham, Massachusetts.

CHEMICAL ANALYSES OF ACD SOLUTION

The contents of ACD packs were analyzed for volume of solution, concentrations of citric acid, trisodium citrate (based on Na^+ measurements), dextrose, and hydrogen ions. These determinations were done as routine quality control procedures by methods described in the *Pharmacopoeia*. All determinations were made on one pack selected at random from each autoclave load. The data herein reviewed were obtained on 1,000 consecutive loads. This summary represents performance on approximately 600,000 packs consecutively produced during the period from 1 June 1956 to 24 September 1958.

The following calculations were made for each category: mean, standard deviation, coefficient of variation, and frequency distribution based on the actual arithmetic mean of each group of 100 tests. The mean, standard deviation, and coefficient of variation of each group of 100 consecutive tests were normalized to 100 per cent of the National Institutes of Health standard value, thus permitting calculation of mean, standard deviation, coefficient of variation, and frequency distribution for the entire series. The results are shown in Table I.

The arithmetic mean for volume, citric acid, trisodium citrate and dextrose concentrations, and *p*H were within the range of ±1 per cent of standard value. The coefficient of variation for each category was less than 1.5 per cent. Since the analytic method of computing frequency distribution is such that all values lie within ±3 standard deviations, it can be seen by reference to Table

I, that for each category the extremes of variation lie well within the acceptable limit of ±5 per cent of the National Institutes of Health requirements.

IN VIVO POSTTRANSFUSION SURVIVAL TESTS ON NORMAL HUMANS OF AUTOLOGOUS RED CELLS OF ACD BLOOD COLLECTED IN PLASTIC PACKS AND STORED FOR 21 TO 23 DAYS AT 4±1 DEGREE C.

Thirty-nine tests were made on plastic bags fabricated from 14 consecutive batches of plastic during the 4 year period from 1 January 1955 to 31 December 1958. The total number of bags produced during this period was 1,399,446, as shown in Table II.

Posttransfusion studies of autologous red cells were made by the radioactive chromium (Cr^{51}) method of Gibson (2). This test is a direct measurement of immediate posttransfusion survival of the infused cells. The packs selected for testing had been autoclaved for from 1 to 7 weeks prior to the collection of blood. All bloods were stored for from 21 to 23 days after collection at 4.0 ±1 degree C.

The lot numbers of plastics released for production during the 4 year period covered by the testing are listed in Table III. The experiment number, date of transfusion, and immediate red cell survival, expressed both as actual per cent and as a per cent of the National Institutes of Health minimum permissible survival (70 per cent), are tabulated. The average survival was 83.0 per cent, with a standard deviation of 11 per cent, and a coefficient of variation of 13 per cent. Eleven of these experiments have been reported previously (6).

The results are shown graphically in Figure 1. It should be noted that 15.4 per cent of the values are above 90 per cent survival; 59 per cent between 80 and 90 per cent, 20.5 per cent between 70 and 80 per cent, and 5.1 per cent below 70 per cent.

Figure 2 shows the frequency distribution and the cumulative relative frequency curve for the data in Table III. The data plotted represent the actual immediate survival expressed as a per cent of the National Institutes of Health minimum permissible survival (70 per cent). It will be noted that the mean of 83 per cent survival corresponds to 118 per cent of the National Institutes of Health minimum value. The curve is reasonably symmetric, in spite of the two low values obtained, as shown by the fact that the intercept on the cumulative relative frequency curve with the 50 per cent median value coincides closely with the arithmetic mean.

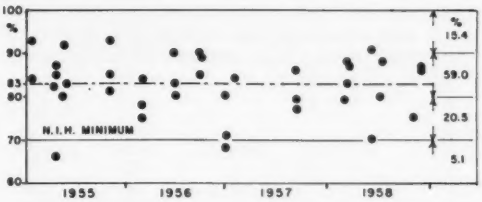

FIG. 1. Posttransfusion survival. Each point represents the results of an autologous transfusion of red cells of ACD whole blood stored in plastic packs for 21 to 23 days at 4±1 degree C. Packs selected at random for testing were from 14 consecutive batches of plastic used during the 4 year period.

LONG TERM STORAGE CHARACTERISTICS OF PLASTIC BAGS

These studies were made to show the effect of long term storage on Fenwal plastic packs. No data have hitherto been pub-

TABLE I.—SUMMARY OF CONFORMANCE TO NATIONAL INSTITUTES OF HEALTH REQUIREMENTS OF ACD SOLUTION IN PLASTIC PACKS

	Volume	*Citric acid*	*Tri-sodium citrate*	*Dextrose (U.S.P.)*	*pH*
Mean*	100.83	100.52	99.55	99.01	100.0
C.V. in per cent	0.92	1.26	1.27	1.04	—
C.V. X 3±	2.76	3.78	3.81	3.12	—

*As per cent of N.I.H. standard.
Consecutive production during the period from 6/1/56 to 9/24/58, totalling approximately 600,000 packs.

TABLE II.—PRODUCTION OF FENWAL BLOOD PACKS FABRICATED FROM FENWAL PLASTIC 6-090, 1 JANUARY 1955 TO 31 DECEMBER 1958

	JA2C	*Total*
1955	79,150	100,959
1956	217,251	242,632
1957	222,704	373,742
1958	260,340	682,113
Totals	779,445	1,399,446

TABLE III.—IN VIVO POSTTRANSFUSION SURVIVAL OF RED CELLS OF ACD BLOOD COLLECTED IN PLASTIC PACKS AND STORED 21 TO 23 DAYS AT 4±1 DEGREE C.

Plastic Lot No.	*Exp. No.*	*Date of Tr*	*Per cent survival (1)*	*Per cent of N.I.H. minimum (2)*
	5	1–26–55	93	133
4607	7	1–26	84	120
	14	4–4	85	122
4657	16	4–5	66	94
4666B	20	5–11	80	114
4666	18	4–13	87	124
	19	4–15	83	119
	21	5–19	92	132
4686B	23	5–25	83	119
4923	32	9–27	93	133
	35	9–28	85	122
	36	9–29	81	116
	53	3–12–56	78	112
5068	54	3–12	75	107
	58	3–13	84	120
	60	7–3	90	129
5391	61	7–7	83	119
	62	7–13	80	114
	63	10–4	90	129
5548	65	10–10	85	122
	66	10–18	89	127
	71	1–7–57	68	97
15605	73	1–29	71	100
	74	1–31	81	116
	75	2–19	84	120
	85	9–19	79	113
15428	86	9–24	86	123
	87	9–27	77	110
	89	3–4–58	79	113
15906	90	3–11	88	126
	91	3–18	83	119
	92	3–20	87	124
	93	6–20	70	100
15936	94	6–30	91	130
	95	7–3	80	114
	96	7–4	88	126
	105	11–28	75	107
16768	106	12–1	87	124
	107	12–9	86	123
Mean			83.0	118.0
S.D.			11.0	
C.V.			13.0	

(1) Immediate posttransfusion survival.
(2) N.I.H. requirements are that not less than 70 per cent of infused red cells be viable after storage for 21 days at 4 to 10 degrees C.

lished on the effects of long term storage on either plastic or glass blood containers. The present Fenwal plastic No. 6-090 was tested from October 1954 to November 1955. Clinical trials were done at the Peter Bent Brigham Hospital from April 1955 to November 1955. Quantities of bags manufactured from the first lot of plastic accepted through the previously reported (7) screening procedures were set aside for subsequent testing after shelf aging. These bags were stored under typical warehouse conditions under control of the Massachusetts Civil Defense Commission and were exposed to seasonal ambient temperatures of 50 to 95 degrees F. Four experiments were carried out at 11 days, 3 at 22 months, and 4 at 48 months after autoclaving.

After removal from storage, the bags and cans were examined carefully for signs of fungal growth and deterioration of materials. The following tests were then made on the bags and the contained solution:

I. Chemical—(a) sodium analysis; (b) dextrose analysis; (c) *pH*; (d) volume; (e) chloride analysis; (f) spectrographic analysis of plastic; (g) spectrographic analysis of solution.
II. Biologic—(a) in vivo survival of red cells; (b) toxicity of solution; (c) pyrogenicity of solution.
III. Bacteriologic—(a) sterility of solution.
IV. Physical—(a) needle sharpness; (b) security of donor tube to needle.

METHODS

Sodium concentration was measured with a Baird flame photometer using an internal lithium standard. Trisodium citrate was calculated by a conversion factor. Citric acid was measured by the method described in the *Pharmacopoeia*. Dextrose analysis was made with a standard Rudolph polarimeter. *pH* determinations were made on a Beckman model H *pH* meter. Chloride analysis was performed according to the method of the *Pharmacopoeia*.

Spectrographic analyses for trace metals were performed as follows: Strips of plastic were cut from the bags and after cleaning in distilled water were decomposed with concentrated nitric acid and hydrogen peroxide. After complete decomposition, the excess peroxide was boiled off and the solution slowly evaporated. Before complete dryness was reached, high purity graphite was added to serve as a carrier for the residue and as a spectrographic buffer. Evaporation was continued to dryness followed by general weakness to decomposed

nitrates. The resulting graphite-residue mixture was removed from the dish and carefully ground in an agate mortar. Portions of this residue were analyzed spectrographically, the material being burned in a direct current arc, and the spectra recorded in the range from 2,100 to 8,500 angstrom units.

For the spectrographic analysis of the ACD solutions, aliquots of the contents from 4 to 8 bags were evaporated to dryness in pyrex glassware. The organic material was decomposed by gentle ashing, and the walls of the container washed down by refluxing with nitric acid. High purity graphite was added to serve as a carrier and the solutions were then evaporated to dryness. The resulting dry graphite-residue mixture, after thorough grinding, was analyzed spectrographically, employing the 10 ampere direct current arc. Equal weights of the graphite-residue mixture were taken so that the resulting spectra were directly comparable. The spectra were recorded in the range from 2,100 to 8,500 angstrom units. The spectrographic estimates were made on the original sample basis. The relative concentration of each element was estimated among the various samples, the lowest concentration being designated as to unity.

Cells were measured by the Cr^{51} method of Gibson (2). Toxicity, pyrogen, sterility tests, and safety toxicity were performed according to the *Pharmacopoeia of the United States*.

RESULTS

Visual examination of the bags and cans after 4 years of storage revealed the following: (1) plastic clear and flexible; (2) donor tube slightly stiff but usable and sealable; (3) ACD solution crystal clear; (4) label dry and firmly adherent to the bag; (5) needle sharp, with no evidence of rust or corrosion; (6) polyethylene bag clear and unaffected; (7) cans: rust, minor and only on soldered seams, and pitting, minor; (8) no mold growth.

Results of the chemical analyses of the ACD solution contained in bags stored 11 days, and 22 and 48 months are shown in Table IV. The slight variations in all measurements over the entire storage period are well within the limit of error of the techniques employed and hence are not significant.

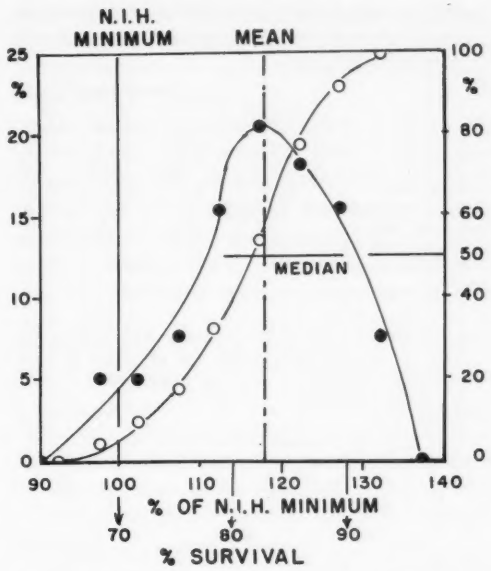

FIG. 2. Frequency distribution (●) and cumulative relative frequency (○) are plotted as percentages of the minimum survival value of 70 per cent of the National Institutes of Health. The arithmetic mean corresponds to 118 per cent of this value.

Spectrographic analyses of plastic showed no significant differences between results obtained in 1955 and in 1959. There were less than 10 parts per million of sodium, magnesium, aluminum, silicon, chromium, manganese, iron, copper, silver, sulfur, and lead. Elements checked for and not found were beryllium, phosphorus, titanium, nickel, cobalt, zinc, arsenic, lithium, molybdenum, cadmium, antimony, iodine, tungsten, and bismuth.

The concentration of elements was higher in the pooled ACD solutions than in the plastic. Sodium was detected within the expected range. In the analysis made in 1957, aluminum, calcium, tin, and barium were present at approximately 100 parts per

TABLE IV.—ANALYSES OF ACD SOLUTION CONTAINED IN PLASTIC PACKS STORED DURING A 4 YEAR PERIOD

		*Storage period**		
	ACD-A U.S.P.	*11 days*	*22 months*	*48 months*
Volume, ml.	75.0	75.0	74.3	74.8
*p*H	4.95	4.80	4.90	4.85
Sodium, mEq./l.	224.0	231.0	223.0	227.0
Trisodium citrate, gm./l.	22.0	22.7	21.6	22.3
Citric acid, gm./l.	8.0	8.2	8.4	8.1
Dextrose U.S.P. gm./l.	24.5	24.9	24.6	25.6
Chloride, p.p.m.	25	<35	<35	<15

*Stored, packaged 4 to a can, at room temperature.

TABLE V.—IN VIVO SURVIVAL OF RED CELLS OF ACD BLOOD COLLECTED IN PLASTIC PACKS STORED DURING A 4 YEAR PERIOD

Experiment No.	*Per cent survival*
STORED 14 DAYS*	
5	93
7	84
14	85
20	80
STORED 22 MONTHS	
76	75
81	74
83	84
STORED 48 MONTHS	
109	92
110	85
111	83
112	75
Mean, per cent	83
S.D.	6.6
C.V.	7.9

*All packs from plastic 6–090, lot 1–5–1. Stored 4 to a sealed can at room temperature.

million; silicon, copper, and iron at from 100 to 10 parts per million; and lead at less than 10 parts per million. Elements checked for but not found were lithium, beryllium, phosphorus, vanadium, chromium, nickel, cobolt, zinc, arsenic, zirconium, molybdenum, cadmium, indium, antimony, tungsten, and thallium. The analysis made on pooled solutions, after 2 years' exposure to the plastic, showed no significant changes.

Results of the in vivo survival tests are shown in Table V.

The range of percentage survival at 11 days was from 80 to 93, averaging 85.4; at 22 months, 74 to 84, averaging 77.7; and at 48 months, 75 to 92, averaging 82.5. The arithmetic mean for the 11 experiments was 83 per cent with a standard deviation rate of 6.57 per cent and a coefficient variation rate of 7.9 per cent. Both the range and mean compare favorably with the series shown in Figure 1.

The results of the pyrogen, sterility, and safety toxicity tests were negative without exception.

Sharpness tests made on the needle showed an average of 3.4 ounces, on a spring scale, for penetration of a polyvinyl chloride film 16 mils thick. This is a nominal limit for acceptability. Tests made on the security of the donor tube to the needle showed an average pull off requirement of 19 pounds. The minimum pull off requirement is 10 pounds. Storage had not affected these two requirements.

DISCUSSION

The degree of uniformity of the results obtained in the analysis of 14 batches of Fenwal plastic 6-090 during the 4 year period of observation clearly indicate the uniformity of the composition and physical characteristics of the plastic used for fabrication of blood packs during this period. Any serious deviation from specifications in composition and surface characteristics of these 14 batches would unquestionably have been reflected in a far less uniform series of survival results.

The series of in vivo survival studies herein reported is the largest to be published on a specific plastic formulation fabricated into blood transfusion equipment. A search of the literature reveals nothing comparable on plastic or glass, in terms of both number of experiments and the observation period.

The standard deviation of 11 and coefficient variation of 13 per cent would seem, at first glance, to be quite high. Nevertheless, this order of magnitude of spread is consistent with other measurements of biologic variation. Thus, the standard deviation of blood volume in a large series of normals is approximately 15 per cent (1). Other hematologic measurements such as red blood cell count and hematocrit in normals show a somewhat less, but nevertheless large standard deviation, probably

because methods for determining red count and hemoglobin have a less intrinsic error than do methods of measuring blood volume.

With regard to the two experiments showing immediate survival below 70 per cent, careful review of the data has shown these to be technically acceptable experiments. In both instances, these subminimum results were obtained in 1 out of 4 experiments performed on a particular batch of plastic. Since the Food and Drug Regulations stipulate that not less than 3 out of 4 tests on any batch must be above 70 per cent, these 2 were considered acceptable.

It is not unusual, and in fact to be expected, that in a large series of biologic measurements such as herein reviewed, a rather wide range of values above and below the mean will be encountered. This is because of the known intrinsic error of the method employed, which may in individual cases be as much as ±5 per cent. A large variation in individual response to the infusion of stored red cells, even though each experiment was an autotransfusion, i.e., the recipient's own cells were stored, tagged with Cr^{51} and returned to the same individual's circulation, is to be expected. Studies by Shemin of the life span of normal human red cells show a range of from 90 to 140 days, and this extreme variation may well account for the 2 low values obtained in spite of the fact that all preliminary tests showed the hemoglobin and hematocrit of these individuals to be normal.

Strumia has recently reported in vivo survival tests in humans of ACD blood stored for 21 days in standard glass bottles. In 8 experiments using the Cr^{51} (2) method, the range of values was from 52 to 93 per cent, the mean being 70 per cent. However, only 2, or 25 per cent of the total series, were above the 70 per cent level, whereas 6, or 75 per cent of the values, were 70 per cent or below.

Comparison of these data with those herein reported clearly indicate not only the superiority of ACD blood stored in plastic bags over ACD blood stored in glass bottles, but also the higher degree of uniformity of performance to be expected in routine blood bank use.

The higher concentration of trace elements found in the ACD solution than in the plastic might, at first glance, seem to be evidence of leaching of metals from the plastic. Closer examination of the data reveals no correlation between concentration of a definite element in plastic and solution during a 4 year period. It is far more probable that contaminants in the reagents used in the preparation of the ACD are responsible.

The constancy of the composition of the ACD contained in the bags, even after shelf storage for a period of 4 years is clear evidence that there is no significant interaction between the ACD solution and the plastic material.

SUMMARY

1. The results of tests designed to assay the chemical, physical, and biologic properties of a plastic used for fabrication of blood containers during a 4 year period are presented.

2. Spectrographic analysis of the plastic showed no trace element to be present in excess of 10 parts per million. No interaction between solutes of ACD and plastic occurred during a 4 year period of shelf storage as evidenced by no significant change in concentration of any trace element found.

3. Thirty-nine in vivo red cell survival experiments by the radiochromium method in humans, done on blood packs fabricated over a 4 year period from 14 consecutive batches of material, showed a range of from 68 to 95 per cent with an arithmetic mean of 83 per cent, and a coefficient of variation of 13 per cent. Fifteen per cent of the values were 90 per cent or above; 59 per cent between 80 and 90 per cent; 20 per cent between 70 and 80 per cent, and 6 per cent below 70 per cent. The variations were randomized throughout the analyses and showed no correlation with any particular batch of plastic.

4. Analysis of data from blood packs fabricated from the first batch of approved plastic showed no significant change in volume or composition of the contained ACD solution, chemical and physical characteristics of the plastic, or maintenance of viability of red cells of blood stored 21 days at 4± 1 degree C. at 22 and 48 months after autoclaving from corresponding control measurements obtained 11 days after autoclaving.

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CARCINOMA IN SITU OF THE UTERINE CERVIX

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THE TOPOGRAPHY and histology of carcinoma in situ of the cervix as revealed by cone biopsy are reported. The most frequent site of involvement was the region of the external cervical os. The frequency of residual tumor at hysterectomy after cone biopsy of the cervix with carcinoma in situ is demonstrated. An unusual case is reported of carcinoma in situ with minimal stromal invasion, extensive lymphatic permeation, and lymph node metastases.

METHODS AND MATERIALS

Three hundred and four biopsies were taken in association with an extensive cytologic survey for the incidence of clinically unsuspected carcinoma of the cervix, as reported previously (7). Sixty-three cone biopsies were selected for this study, the criteria for selection being the availability in a fresh state, the adequacy of the specimen, and the presence of carcinoma in situ or a closely related lesion. The specimens were studied for the topographic distribution of the lesion, 22 completely and 41 in a modified form. In most cases, 2 cross sections were taken at the apex of the cone and then a longitudinal incision was made through the length of the endocervical canal. The specimens were fixed for 24 hours in 10 per cent neutral formalin or Zenker's fixative. Parallel segments were cut in a radial fashion in which the endocervical canal was the center.

No cross sections of the apex of the cone were prepared if the cones were distorted or too small. From 8 to 10 segments were prepared from each specimen. In 22 cases of carcinoma in situ, the blocks were carefully oriented as to the surfaces of the adjacent segments so that the end section of one block was properly related to the first section of the adjacent block. Step-serial sections were cut, and each tenth section was stained with hematoxylin and eosin. An average of 80 to 100 slides were prepared from each case.

In 30 cases of carcinoma in situ the apposing lateral surfaces of the adjacent blocks were not necessarily oriented, but all blocks were identified as to their composite relationship to each other. Step-serial sections were cut halfway through the blocks and each tenth section was stained with hematoxylin and eosin. These specimens, although not as informative as the 22 previously described, contributed significantly to this study.

The diagnoses of carcinoma in situ, atypical hyperplasia, and squamous metaplasia conformed to the criteria of Reagan and associates (5, 6). Three experienced pathologists reviewed representative slides from each case to insure accuracy of diagnosis. The diagnosis of carcinoma in situ was made only upon unanimous agreement. Lesions were classified as borderline atypical hyperplasia if the specimens closely approximated the criteria for carcinoma in situ but lacked unanimous agreement for the latter diagnosis.

Eleven cone biopsies revealed atypical hyperplasia, 9 of which were of borderline type. These specimens were examined as described.

The location and extent of the lesions were schematically outlined for each case (Fig. 1). The dimensions of the lesions in a segment were determined with an ocular whose visual field had been measured. These dimensions were blocked out on the outline for the corresponding segment. The measurement, although approximate, was valuable in delineating the lesions relative to one

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TABLE I.—INCIDENCE OF CONTINUOUS INVOLVEMENT OF MULTIPLE SEGMENTS OF CERVIX BY CARCINOMA IN SITU

Case No.	*No. of segments*	*Case No.*	*No. of segments*
1	3	12	5
2	6	13	6
3	1	14	1
4	8	15	4
5	8	16	3
6	2	17	4
7	5	18	2
8	6	19	5
9	6	20	1
10	8	21	10
11	5	22	7

another and in furnishing a useful visual outline of the approximate extent and location of the involved epithelium. Of the 22 cases of carcinoma in situ with complete step sections through all blocks, 15 involved the region of the cervical os and adjacent endocervix. In 2 cases, the lesion involved the portio as well as the region of the os and endocervix. This fact was recognized by the extension of the lesion onto the portio for at least 0.5 centimeter beyond the squamocolumnar junction. There were no cases of involvement of the portio alone, whereas in 5 cases, only the endocervix was the seat of carcinoma in situ. In the latter cases, there was widespread involvement of the endocervices, the lesions extending close to the external cervical os, often within 0.5 centimeter. The location of the carcinoma in situ was similar in the 30 cone biposies with only partial step-serial sections.

Multicentric foci of carcinoma in situ were present in 3 of 22 cone biopsies and questionable in 4. In the latter specimens, there were areas of denuded epithelium which were possibly involved by carcinoma in situ so that the discontinuous distribution might have been artefact.

A continuous sheet of carcinoma in situ was frequently found in several adjacent segments of the cone, thus demonstrating the extensive involvement of the cervical epithelium. Table I demonstrates the incidence of continuous involvement of multiple segments in 22 cone biopsies studied by complete step sections. In 4 of the specimens carcinoma in situ was found in only 1 or 2 segments. The lesion was limited to 1 or 2 segments in 16 of 30 specimens with only partial step-serial section.

Foci of atypical hyperplasia and squamous metaplasia were found in 14 of 22 cases. These lesions were usually continuous with carcinoma in situ or nearby. Usually the zones of atypical hyperplasia and squamous metaplasia were caudad to the intraepithelial carcinoma, frequently being located between the portio and the carcinoma.

Forty-six cases were reviewed for the type of cells in the intraepithelial carcinoma. Twenty-eight were composed predominantly of polyhedral cells, 15 of a mixture of polyhedral cells and variants of oval to spindle cells, and 3 chiefly of spindle cells.

There was endocervical gland involvement by tumor in 46 of 52 specimens.

An inflammatory reaction was inconstant near the intraepithelial carcinoma. It was near the tumor in 24 of 39 cases and elsewhere in the specimens in 16 of 39 cases. The inflammatory cells were chiefly plasma cells and lymphocytes.

There was infrequent superficial keratin and cell differentiation in the neoplastic lesions; rare foci occurred in 21 of 41 cases. Superficial shrinkage and pyknosis of nuclei with loss of cell boundaries mimicked parakeratosis. Keratin was extremely rare in the lower layers of the tumor and in the foci of endocervical involvement. In the latter, the keratin was centrally located. On occasion there was differentiation and keratin formation in areas of superficial invasion.

Mitotic activity was quite variable in the intraepithelial tumors, averaging between 3 and 4 divisions per high power field. The number of mitoses in some areas was less than 1 per high power field, and, in 1 case, as frequent as 15 per high power field.

There was early stromal invasion in 2 cases and questionable invasion in 3 of 52 carcinomas in situ. One of the specimens with superficial stromal invasion showed lymphatic involvement. Invasive squamous cell carcinoma was concomitant with in situ carcinoma in 2 specimens.

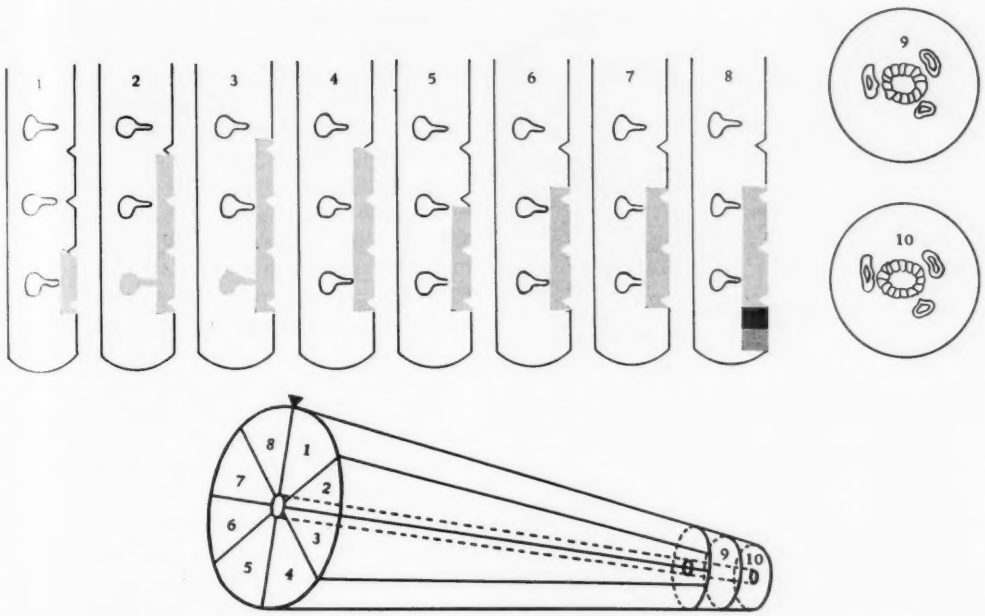

FIG. 1. Example of diagram for topographic study. Black portion indicates atypical hyperplasia, light gray portions indicate carcinoma in situ, and the one darker gray portion indicates squamous metaplasia.

Hysterectomy specimens were available for examination in 22 of 52 cases of carcinoma in situ studied topographically. Residual intraepithelial carcinoma was demonstrated in 5. The adequacy of the initial excision could not be satisfactorily evaluated in 2 of these cases because of deficient segments of epithelium in 1 and difficulty in orienting the sections in the other. In a third case, the cone biopsy revealed superficial stromal and lymphatic invasion in association with carcinoma in situ. In the remaining 2 cases, the initial cone biopsies appeared to have adequately removed the lesions and there was no evidence of stromal or lymphatic invasion.

Residual carcinoma in situ was found in 17 specimens not included in the topographic study. The initial diagnosis had been made mostly on small biopsy specimens and on 3 cone biopsies.

In the cases of borderline atypical hyperplasia, the lesions were chiefly in the endocervix and there was frequent glandular involvement. Mitotic activity averaged less than 1 cell per high power field. Polyhedral cells were predominant in the foci of atypia. There was an inconstant inflammatory reaction associated with the lesions. Superficial cell differentiation occurred more frequently than in carcinoma in situ. There was rare superficial keratin formation.

DISCUSSION

Carcinoma in situ was found chiefly in the external cervical os and adjacent endocervix. The portio was rarely involved (2 cases) in conjunction with the os and endocervix, and there were no cases of tumor exclusively in the portio. There are diverse reports about the topographic distribution of cervical intraepithelial carcinoma. Foote and Stewart studied 27 cases and found 10 with lesions of the portio, 14 involving the portio and endocervix, and 3 limited to the endocervix. Thus, almost one-third of their cases were tumors of the portio only. In 118 cases, Fennell found 100 per cent endocervical in-

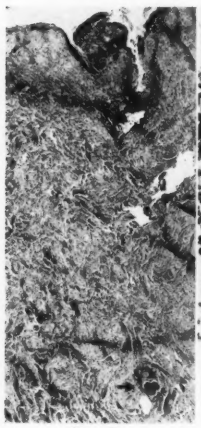

FIG. 2.

FIG. 3.

FIG. 2. Tumor in stroma and adjacent lymphatic (arrow) in association with carcinoma in situ. × 9.

FIG. 3. Higher magnification of tumor in stroma and adjacent lymphatic. × 162.

volvement and 22 per cent with involvement of the adjacent portio. Przybora and Plutowa found the distribution of in situ cancer of the cervix similar to that of Foote and Stewart. There were 27 lesions in the portio, 30 involving both portio and endocervix, 12 in the endocervix, and 8 in the os. Carson and Gall found the lesions chiefly in the endocervix with only rare extension to the portio.

Przybora and Plutowa have carefully delineated the location of the in situ lesions by making drawings of fivefold enlargements of histologic sections with a photographic magnifier. They have attempted to make a correction in their measurements for tissue shrinkage as well as for the poorly defined boundaries of the cervical os. There remains the problem of evaluating the discrepancies in these series.

The location of the cervical os is difficult to delineate. The squamocolumnar junction does not necessarily identify the junction of the endocervix and the portio, because squamous epithelium extends irregularly into the endocervix. Przybora and Plutowa have estimated that the cervical os is a circular area that is 1.2 centimeters in width if the hypothesis is accepted that the squamocolumnar junction of the endocervix and portio is a zone rather than a finite junction. In addition, correction is made for error in identification of the zone and tissue shrinkage. If there is agreement with this concept, then most investigators probably have located the in situ lesions in essentially the same area, namely, in the region closely associated with the cervical os with extension into the endocervix and portio. Thus, what some investigators may have identified as endocervical carcinomas may actually have been orificial carcinomas. However, Przybora and Plutowa found approximately one-third of the lesions in their cases in the portio. Inasmuch as these sites were identified, even after correcting for the potential errors enumerated, the premise must be accepted that there is a variation in location of carcinoma in situ. The lesion usually is in the region of the cervical os but it may be found in the endocervical canal. Hence, a punch biopsy of the cervix may miss the lesion, whereas the cone biopsy with its larger sample of tissue may be successful in demonstrating the in situ cancer.

Although carcinoma in situ was frequently found in several segments of a cone biopsy, 22 out of 52 specimens contained the lesion in only 1 or 2 segments. Therefore, 4 quadrant biopsies or the so-called "ring biopsy" at the cervical os are deemed to be less desirable than the cone biopsy which will ensure a more adequate sample, especially of the endocervix.

Hysterectomy revealed carcinoma in situ in 5 of 22 cases included in the topographic survey and in 17 other cases. This fact demonstrates the necessity for hysterectomy or careful cytologic follow-up when the cone biopsy has revealed intraepithelial carcinoma.

There are two groups of cases in which carcinoma in situ may be associated with invasive carcinoma. In one group are the cases of in situ carcinoma with focal superficial stromal invasion. This lesion must be contrasted with the obviously invasive squamous cell carcinoma with in situ carcinoma

at its periphery in the other group, since the prognosis of the former group is usually similar to that of an uncomplicated case of intraepithelial carcinoma.

Younge, Hertig, and Armstrong have emphasized the rarity of lymphatic spread from carcinoma in situ of the cervix. Our experience has been similar. However, we have had 2 unusual cases. In 1, there was superficial stromal invasion and lymphatic involvement. The other case, not included in the topographic survey, was remarkable because of clumps of tumor in superficial lymphatics with only minimal evidence of carcinoma in situ and only 1 minute focus of invasive tumor adjacent to a lymphatic (Figs. 2 and 3). Examination of step-serial sections was noncontributory. There were foci of deficient endocervical mucosa, but the underlying stroma failed to show invasive carcinoma. Presumably, there was a small focus of stromal invasion which had promptly invaded and permeated the superficial lymphatics.

Despite the minimal involvement of the cervix, a radical hysterectomy was performed because of the finding of metastatic tumor in obturator and periaortic lymph nodes at hysterectomy. The only residual tumor in the uterus was in lymphatics at the site of the cone biopsy (Fig. 4).

In Fennell's experience, the cases of carcinoma in situ with superficial stromal invasion showed differentiation with keratinization and pearl formation at the sites of invasion. He has also noted that the invasion occurred at multiple sites. In our series, differentiation and keratinization have been seen less frequently in invasive foci than in Fennell's experience and there have not been multiple foci of stromal invasion.

There was frequent involvement of endocervical glands by in situ carcinoma. Usually, these sites of tumor could be differentiated from invasive cancer by the well defined margins of the nests of tumor cells and the superficial location of the tumor. Glandular involvement does not alter prognosis, because there is no stromal invasion and hence little likelihood of lymphatic involvement. We have rarely seen stromal invasion from an involved gland.

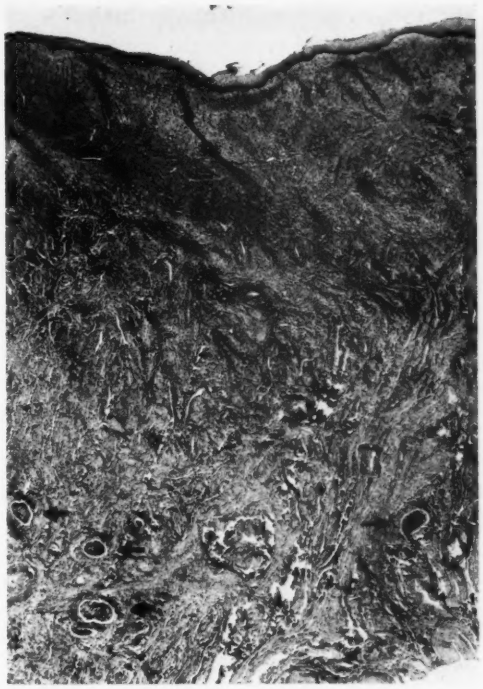

FIG. 4. Residual tumor in lymphatics (arrows) in hysterectomy specimen. × 15.

Although some investigators have been impressed with the incidence of inflammatory reaction in association with in situ cancer, it occurred in only 61 per cent of our series. It was more constant in the cases of stromal invasion of both superficial and deep type.

The marked variability of mitotic activity in our cases is similar to the experience of Stevenson and Scipiades. These investigators have emphasized the greater diagnostic significance of anaplasia over mitotic activity in the identification of intraepithelial carcinoma.

The cells in our tumors were chiefly of polyhedral type or mixtures of these cells with variants of oval to spindle cells. This finding is of questionable prognostic significance, although it has been suggested that

the tumors of predominantly undifferentiated spindle cell type might have a greater invasive tendency. Atypical hyperplasia and squamous metaplasia were frequently concomitant with carcinoma in situ and usually located closer to the squamocolumnar junction. There was an inconstant inflammatory reaction near the tumor. Mitotic activity was only moderately frequent. Often there was glandular involvement by the tumor.

SUMMARY

Histologic and topographic studies have been made on 52 cone biopsies of the cervix containing carcinoma in situ and 11 cases of atypical hyperplasia. Carcinoma in situ occurred predominantly in the external cervical os and adjacent endocervix. Frequently, the tumor grew as a continuous sheet over large areas of the endocervix. However, in a significant number of cases, the tumor was limited to small foci so that cone biopsy was deemed preferable to punch biopsy because the larger sample of tissue more likely would demonstrate the lesion.

Hysterectomies revealed residual carcinoma in situ in 5 of 22 cases included in the topographic survey and in 17 other cases. This observation demonstrates the necessity of hysterectomy or careful cytologic follow-up whenever a cone biopsy has revealed intraepithelial carcinoma.

Stromal invasion was infrequently demonstrated. There were 2 rare cases of carcinoma in situ with lymphatic invasion. In one, the lymphatic permeation was unusually extensive and there were metastases to regional lymph nodes.

Several histopathologic observations are delineated.

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CRANIOBUCCAL ORIGIN, SIGNS, AND TREATMENT OF CRANIOPHARYNGIOMAS

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THIS COMMUNICATION reports a series of 73 histologically verified cystic or solid tumors of craniobuccal origin. The signs, symptoms, and treatment of this type of lesion will be evaluated in the light of the embryology of the hypophysis and pathologic changes occurring in and about the lesion.

Other investigators have designated this type of lesion by the following terms: hypophysial duct, Rathke's pouch, or suprasellar cyst, as well as adamantinoma, ameloblastoma, cholesteatoma, craniopharyngioma, and epithelioma. This varied terminology represents an effort to describe in one or two words the position of the neoplasm, the predominating cell within it, or its embryologic origin. Needless to say, no one term has proved to be quite satisfactory. Because of general acceptance, Cushing's term, craniopharyngioma, has been selected to cover the group of tumors under discussion.

GROSS ANATOMY

The operative and autopsy descriptions of the tumors in this series indicate that outgrowths of the tumor from its site of origin in the pituitary fossa may take any direction once the sellar diaphragm is passed. In the majority of the lesions, the greatest volume of the tumor was cystic. However, in 12 instances, the lesion was found to be solid. In some individuals, the cysts were multilocular, compartmentation being maintained by thin walls, but most frequently there was one predominating cyst. Some cavity linings were flat, but usually there were villous folds with some degree of papillary projection. The capsules varied in thickness, and, accordingly, in appearance. The heavier capsules were gray and firm, whereas the color of the encased fluid transmitted through thinner capsules gave the cyst a greenish or brownish-blue appearance. Many have likened the color and viscosity of the cyst fluid to machine oil. Frequently, the surface shimmered because of contained cholesterol crystals. The solid portion of the tumor was not as heavily encapsulated as the average cyst. Where the tumor made contact with neural tissue, an adherent glial barrier was thrown up which usually precluded surgical resection without jeopardy to the brain and its vascular supply.

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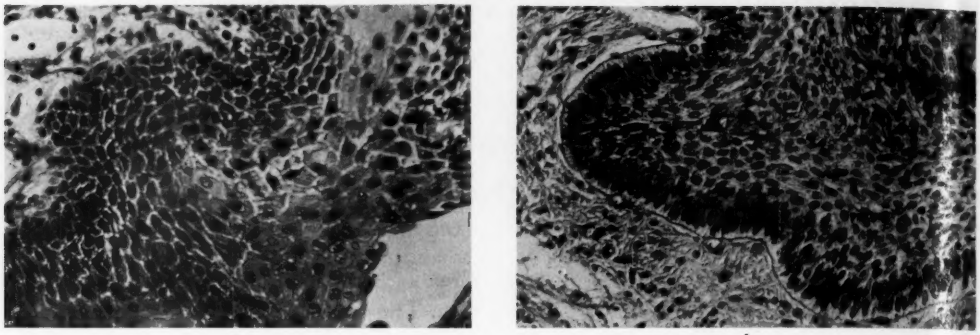
MICROSCOPIC ANATOMY

The predominating cytoarchitecture of the cyst linings was adamantinomatous. Where squamous epithelium was found, there was almost invariably some adamantinomatous tissue nearby. A pure squamous epithelial lining was a rarity in this group of cases. There were no mucoid epithelial cysts as described by Bailey. The two types of linings are illustrated in Figure 1. Frequently, the orderly cytoarchitecture of typical squamous cell linings was interrupted by whorl formation. Cornification and keratinization appeared at the end of the life cycle of this type of cell. In both types of linings there were areas of degeneration which involved the epithelium as well as the stroma. Interstitial deposition of calcium was a constant microscopic finding. In 47 individuals, the process was sufficiently extensive to be identifiable in the



a b

FIG. 1. Photomicrographs of epithelium found in craniopharyngiomas. a, Squamous cell type; b, adamantinomatous type. Hematoxylin and eosin, ×235.

clinical roentgenographic examination, a matter of diagnostic significance. In no instance was the calcification construed as early enamel formation, since it resembled the type seen with tissue degeneration. In one or two specimens actual bone had been laid down, a phenomenon that has been known to follow calcium deposition elsewhere in the body. Doubtless the release of lipids, lipoproteins, mucopolysaccharides, and alkaline phosphatase all played a role in deposition of calcium as well as in the rare instances of aberrant osteogenesis.

EMBRYOLOGIC CONSIDERATIONS

Similarity of the cytoarchitecture of the tooth bud in a 30 millimeter human embryo (Fig. 2) and that of an adamantinomatous craniopharyngioma (Fig. 1, b) surely warrants consideration of the embryologic origin of the tooth and pituitary gland. Since the hypophysis develops from a junction of a ventral outgrowth of the diencephalon with a dorsal diverticulum arising in the midline from the stomodeum at a point immediately anterior to the buccopharyngeal membrane, current investigators are convinced of the pure ectodermal origin of this gland. Their argument is substantiated by the fact that this event occurs while the buccopharyngeal membrane is intact and the anterior neuropore is open. Because the former structure demarcates the oral ectoderm from the pharyngeal endoderm, it is generally believed that the latter type of cell does not contribute to the composition of the pituitary gland. Tilney, in a measured evaluation of his own work as well as that of others, is not as didactic in excluding the possibility of endoderm entering into the formation of the hypophysis. His caution is based on contiguity of the following endodermal structures with the anlage of the gland: the foregut, Seessel's pocket, the notochord, and the premandibular somite. Recent research, primarily directed at determining the nature of the cells involved in tooth bud formation, offers a possible explanation of the origin of adamantinomatous tissue in the patients with craniopharyngiomas. Sellman demonstrated that successful grafting of explants of cranial neural crest, stomodeal ectoderm, and pharyngeal endoderm in the flank of Ambystoma embryos lead to tooth bud formation. However, this phenomenon did not occur if any one of the three cellular elements was not grafted. Wilde's in vitro studies and Levy's more recent in vivo corroboration of Sellman's original work confirm this triad of tissues as being essential to tooth bud formation. Two of the cell types required in these experimental protocols are brought into juxtaposition when a union is formed between the stomodeal ectoderm and the diencephalon. These are

oral ectodermal and cranial neural crest cells which later will form the leptomeningeal envelopment of the pituitary stalk. If, by chance, some minor abnormality in the formation of stomodeal diverticulum permits the inclusion of cells from the pharyngeal endoderm, all three cell types essential to tooth bud formation are brought together and the stage is set for the development of an adamantinoma within the hypophysis. Even if this thesis is later borne out by future explantation experiments in the Amphibia, it will not explain why in certain human beings metaplasia of adamantinomatous or squamous epithelial tissue develops to a degree which proves to be fatal, while in others squamous epithelial cell rests are incidental autopsy findings, 39 per cent according to Carmichael. The answer to this question awaits explanation by future research, as does the reason for the time of appearance of this type of tumor in an individual patient. Figure 3 demonstrates the diversity of age at which the individuals in this group first were operated upon because of the tumor. Careful study of certain of the histories in this group suggests the presence of the tumor for as long as 20 years before the onset of the signs which occasioned admission to the hospital. Certainly, a craniopharyngioma is a true tumor and not a congenital anomaly. No tumor in this series showed the malignant changes reported by Peet.

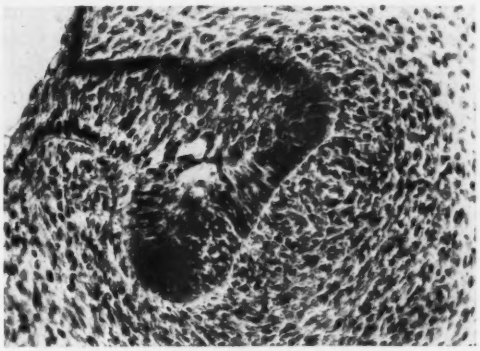


FIG. 2. Tooth bud in 30 millimeter human embryo. Note similarity of cytoarchitecture of this normal structure and that found in the adamantinomatous craniopharyngioma in Figure 1b. Hematoxylin and eosin, ×240.

CLINICAL SIGNS AND SYMPTOMS

These tumors originate on the anterior superior surface of the pituitary gland at or near the level of the sellar diaphragm. Once this structure is eroded, growth may take any direction from this strategic site; therefore, the consequent signs and symptoms will not be consistent nor will the order in which they appear; neither can all be caused by a single mechanical phenomenon. Some are manifestations of generalized intracranial pressure which follows occlusion of the foramina of Monro by an upward extension of the tumor. Others are doubtless caused by direct compression of a contiguous structure and attendant impairment of the local channels for venous return from the capillary bed. Still others arise because of venous congestion in relatively remote tracts and nuclei secondary to compression of the basilar veins. This statement becomes reasonable in the light of the tributaries that compose this venous system. Mettler's succinct description of the formation and course of this anastomotic complex lists the channels of venous drainage that may be impaired by compression exerted by a craniopharyngioma: ". . . the basal vein (vena basalis or Rosenthali), originates on either side of the optic chiasm by the confluence of the anterior cerebral and deep middle cerebral veins. Passing backward it receives tributaries from the anterior perforated substance, optic tract (ventral to which it passes), and from the tuber cinereum. It reaches the basis pedunculi somewhat lateral to the point of emergence of the oculomotor nerve, follows the side of the mesencephalon dorsally, crosses the superior colliculi, and unites with the internal cerebral vein to form . . . the vein of Galen." In all likelihood, compression of the arterial supply has negligible clinical manifestations until the patient is moribund, and compensatory control of the pulse and blood pres-

sure fails because of anoxia in the medulla secondary to increased intracranial pressure.

Since the tumor originates on the anterosuperior surface of the anterior lobe of the hypophysis, at or near the level of the sellar diaphragm, it is understandable that this organ should be affected, as well as the nearby hypothalamus from which it derives innervation. Because a neoplasm is not a precise instrument of destruction, and laboratory investigations show an ever increasing interrelationship between both structures, the signs and symptoms in 38 individuals, which previously would have been attributed to a disturbance of either of the two organs, will be considered together rather than separately. No patients had classic and unrelenting diabetes insipidus. However, a demand for fluids in excess of the usual amounts and associated urinary frequency was observed in 26 and 28 individuals, respectively, indicating a maladjustment of water metabolism. Twenty-three persons had subnormal blood pressure, and in 15 the basal metabolic rate was well below the mean. Varying degrees of the adiposogenital syndrome were recorded in 14 admission physical examinations. Other signs attributable to a hypophysial-hypothalamic disturbance were found in individual patients as follows: dwarfism, 5; cachexia, 3; and polyphagia, 2. Decreased libido in 11 individuals and impotence in 6 others were further manifestations of compression in the hypophysial-hypothalamic area. One patient who endured these last two phenomena for 25 years along with weight loss exhibited dry scaling skin and long-standing loss of all body hair except for thin, fine-textured scalp hair. Gradual loss of vision over a 2 year period, not the latter changes, prompted his initial visit to the clinic.

Anterior and anterolateral extensions of the lesion were responsible for the majority of visual symptoms (68 patients) and signs (59 patients) which head the list of primary complaints and objective findings. However, in certain instances, the causative mechanism was generalized increased intracranial pressure and not localized compression of the optic nerves and chiasm. Eight individuals were blind and 45 showed varying degrees of optic atrophy. Tangent screen testing proved bitemporal hemianopsia in 20 persons, and a homonymous hemianopsia in 5 others. No field defect was detected in 8. The test was not made in 5 others. In the 27 remaining members of the group, the defects ranged from contracted visual fields to preservation of a portion of one of the eight quadrants, or bizarre scotoma patterns. The Foster Kennedy syndrome was seen only 3 times, whereas, bilateral papilledema with bilateral optic atrophy was more common. A survey of ophthalmologic findings revealed that the incidence of optic atrophy without papilledema was more frequent after the first decade. No valid explanation for this discrepancy is forthcoming from this study. Morbid drowsiness was noted in 46 charts, stupor in 12, irritability in 8, and coma in 4. Doubtless, the general congestion of the brain which accompanies increased intracranial pressure was responsible in the main for these signs, as well as for vomiting in 36 persons, pyramidal tract signs in 33, papilledema in 30, cerebellar signs in another 14, and 30 complaints of weakness. However, compression of specific portions of the basilar venous drainage of the brain by the lesion in the absence of increased intracranial pressure might have caused any of these abnormalities. Drowsiness was noted in 10 patients who did not have ventricular enlargement or elevated intracranial pressure. Marked personality changes resulting under similar circumstances further exemplify this mechanism. In one individual, facetiousness reached such a point that the provisional diagnosis was frontal lobe tumor. In another, memory loss, confusion, and confabulation were equally misleading. White and Cobb in 1955 reported a similar experience in persons with large pituitary adenomas, not all of whom had increased intracranial pressure.

A mimetic facial paresis was found in 24 persons, only 3 of whom suffered from an associated hemiparesis. However, in all but 5 of this group, detailed examination revealed signs which implicated the pyramidal tract, cerebellum, or both. The fact that papilledema was detected in only 14 of this group and 8 did not have increased intracranial pressure suggests a compression impairment of the venous drainage of the internal capsule and thalamus. In the case of the others, it is more reliable to ascribe their difficulties to the relative anoxia which accompanies generalized venous congestion associated with intracranial hypertension. Reasonable clinical proof of the mechanism of compression of a portion of the venous drainage of the brain was obtained on more than one occasion by tapping a cyst in an individual, not in this series, who developed a facial palsy whenever the cyst became distended. Each decompression of the cyst was associated with an immediate restoration of normal function which lasted until the fluid reaccumulated.

In this relatively large group of patients, some cranial nerves were affected more frequently than others. Disturbances of the second and seventh cranial nerves already having been discussed, it would seem wise to start rostrally and mention that anosmia was found in 14 individuals. Then moving more caudad, it is interesting to note that there were no individual trochlear nerve disturbances and that the incidence of impairment of function of the third and sixth cranial nerves was relatively low. In the case of the former, the predominating disturbance was anisocoria which could be accounted for on the basis of the deficit in visual acuity in the corresponding eye. Ptosis was found in only 4 persons, and convergence difficulties in an equal number. Restriction of upward gaze occurred in 1 individual without accompanying weakness in the other muscles innervated by the same nerve. Sixth nerve weakness appeared in another 15 examinations. In 3 of these individuals, the intracranial pressure was not

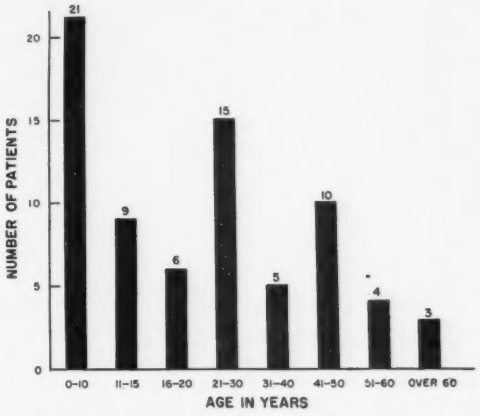


FIG. 3. Chart of age incidence of the 73 patients in this study.

elevated nor were the ventricles enlarged. Therefore, it may be presumed that in the 12 others, abducens nerve disturbances arose as the result of increased intracranial pressure and that in the smaller group, compression by the tumor may have been the causative mechanism. That third, fourth, and sixth cranial nerve palsy did not occur more frequently on the basis of direct compression by the tumor speaks highly for the protection afforded by the tentorium before these nerves reach the cavernous sinus. The neighboring components of the trigeminal nerve were spared, with few exceptions. There were 5 examples of unilateral diminished corneal reflexes, one of hypesthesia in the second division, and 1 of masseter muscle weakness. The cochlear division of the acoustic nerve was grossly impaired in 7 patients. This is not remarkable in view of the fact that they had increased intracranial pressure. Had audiometry been a routine part of the study, this figure would doubtless have been larger. The other cranial nerves were not involved except in the case of hemiparesis. Of interest is 1 patient who showed a picture similar to pseudobulbar palsy. The best explanation for this constellation of signs is venous congestion of the upper brain stem.

Subjective sensory disturbances were limited, for all practical purposes, to the

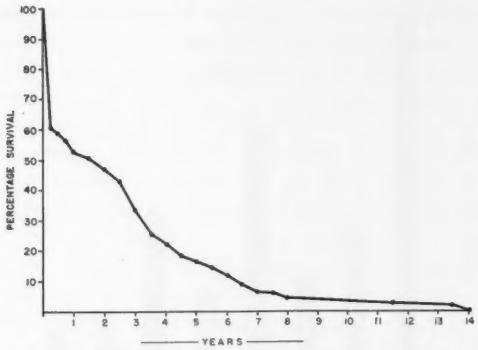


FIG. 4. Percentage survival as a function of time in 53 postoperative patients now dead.

ranking complaints of visual impairment (68 patients) and headache (65 patients).

Two bizarre sensory disturbances worthy of mention probably arose as the result of compression of the thalamic blood supply. In the first instance, a 29 year old female complained of a prickling, crawling sensation over the skin of the face for 3 months prior to hospitalization; in the other, a 10 year old male complained of a spontaneous pain in his left heel, unassociated with any other complaints or physical findings in the lower extremities for 2 months prior to admission.

ROENTGENOGRAPHIC DATA

Fifty-two per cent of the patients in this series showed some roentgenographic evidence of increased intracranial pressure. Erosion of the sella turcica, judged by distortion or destruction of the inner and superior surfaces of the anterior and posterior clinoid processes, was detected in 22 patients. In the pediatric age group, increased convolutional markings and suture separation were common phenomena. However, suture separation in a 21 year old woman with a 5 year history merits individual mention. Atrophy and demineralization of the posterior clinoid processes were frequent findings not necessarily restricted to the pediatric age group. This is not included as a criterion for sella turcica erosion. Radiopaque flecks or small plaques suggestive of calcium deposition within the lesion appeared in 47 roentgenographic studies, a 64 per cent incidence in contrast to the 71 per cent published by Sosman and Putnam. Intrasellar calcification was visible in most cases of sellar erosion and coincident calcium deposition elsewhere within the lesion. Ten of 12 individuals with sella turcica enlargement without erosion showed intrasellar as well as extrasellar calcification. Intrasellar, parasellar, and suprasellar calcification is excellent qualitative evidence. Unfortunately, it is not quantitative. Some of the largest cysts showed only an occasional area of calcification, and that was restricted to the solid portion of the lesion.

No films of the skull were made when any of these individuals were having their first difficulties with headache. For this symptom, temporizing therapy was usually given until the development of other signs and symptoms clarified the situation. A review of the preoperative films and the histories, however, suggests that in certain instances, had lateral films of the skull been added to the fairly frequent requisitions for films of the sinus, a diagnostic degree of sella turcica deformity or intrasellar deposition of calcium might have been detected in certain patients when the cause of the headache was sellar diaphragm tension. Needless to say, operation at this stage would have been more successful.

TREATMENT

The ideal treatment for all neoplasms is total removal, and this would apply in particular to the craniopharyngioma which is a benign lesion. Variability in direction of extension, size, and degree of cystic development precludes a set operative routine, and each surgical attack must be planned in accordance with clinical signs and roentgenographic data obtained from plain films and ventriculograms. Even though calcification gives reasonable assurance to the clinical diagnosis, ventriculography is indicated because it aids in planning the surgical attack. Adherence of solid or cystic portions

of the lesion to vital neighboring structures more than often has precluded complete removal and forced a compromise. It has been the general working principle at this clinic to attempt complete removal but never to force the issue to a point where the risk is unreasonable. Therefore, in the majority of cases, all visible cysts have been evacuated and their walls removed insofar as possible, along with solid portions of the tumor which were readily accessible and not too vascular. In this way, it has been possible temporarily to preserve life in jeopardy from increased intracranial pressure and to restore vision by reduction of the mass occluding the foramina of Monro or impinging upon the individual optic nerves and the chiasm. This policy has led to many incomplete extirpations, but there is a large group of survivors, many of whom have undergone second and third procedures. Recently, Ransohoff has achieved several total resections, including one upon a third attempt. The usual operative approaches have been subfrontal or transventricular. Permanent intraventricular drainage of large cysts, evolved by our colleague Scarff, has proved to be successful if the criteria are followed that have been established by him. Likewise, limited experience with tapping and drainage of recurrent cysts supplemented by a bilateral Torkildsen-type ventriculocisternostomy has relieved signs and symptoms and prolonged life. Seventy-one of the patients in this group have been operated upon. The lesion in the 2 individuals too ill on arrival to undergo surgery was verified at autopsy. The surgical mortality was 29 per cent. This figure was inclusive for second and third attempts, which, on the whole, have carried a greater risk. The over-all risk of an initial operation amounted to 22 per cent. This figure includes patients operated upon over 20 years ago. Advances in anesthesia, means of preventing adrenocortical failure, and controlled hypothermia are reducing the risk.

Figure 4 shows the percentage survival as a function of time in 53 patients now dead.

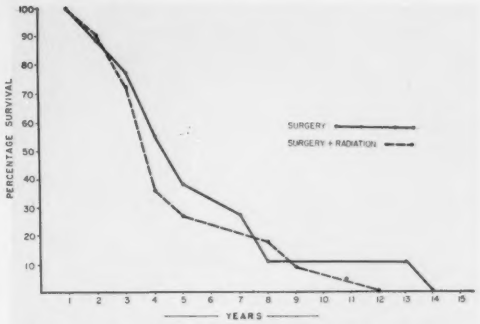


FIG. 5. Graph which shows survival as a function of time in two groups of patients, now dead, all of whom survived the first postoperative year. Eighteen individuals were treated by surgery and 11 received irradiation in addition.

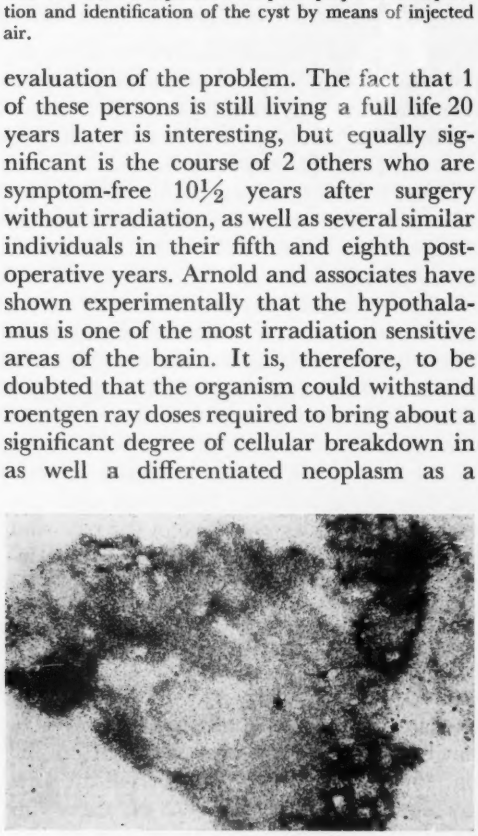
Some of these patients underwent multiple operations. The first two procedures had an identical mortality rate, 24 per cent in these particular individuals, which rose to 33 per cent with the third operation.

Despite the cytology of the lesion, irradiation directed at residual tumor is thought to be beneficial by some. Leddy and Marshall quote the experiences and opinions of others in regard to the efficiency of roentgen irradiation on craniopharyngiomas. They believe that this form of treatment prevents fluid formation within the cyst. This view is not universally accepted in this clinic. Individual surgeons have followed their personal convictions in regard to adding this supplementary treatment after the surgical attack. Twenty-five of the reported patients have been treated by roentgen irradiation as well as surgery. Four of these individuals did not survive the first postoperative year. Figure 5, a graph of percentage survival as a function of time, does not show convincing evidence in favor of the addition of roentgen ray therapy to surgery. These data are derived from 29 patients, all dead, who survived the first postoperative year. Eleven of these individuals received irradiation and 18 did not. Further follow-up of 10 individuals now surviving over a year who have received postoperative roentgen therapy may aid in

FIG. 6. The cyst outlined with air and pantopaque. The Y^{90} Cl_3 was injected with pantopaque after aspiration and identification of the cyst by means of injected air.

evaluation of the problem. The fact that 1 of these persons is still living a full life 20 years later is interesting, but equally significant is the course of 2 others who are symptom-free 10½ years after surgery without irradiation, as well as several similar individuals in their fifth and eighth postoperative years. Arnold and associates have shown experimentally that the hypothalamus is one of the most irradiation sensitive areas of the brain. It is, therefore, to be doubted that the organism could withstand roentgen ray doses required to bring about a significant degree of cellular breakdown in as well a differentiated neoplasm as a craniopharyngioma. However, it is always possible that in the cases reported as having been improved by irradiation, some unknown biologic factor may have been influenced by intermittent doses of roentgen rays.

When a cyst appears in a lesion previously proved to be unresectable, aspiration of the cyst and direct exposure of the tissue of its walls to beta radiation may prove to be a more useful therapeutic adjunct than irradiation with roentgen rays. Leksell and Lyden and Wycis and co-workers report good results with radioactive phosphorus; Woods and Tozer have employed radioactive gold. A colloidal suspension of radioactive yttrium in the form of Y^{90} Cl_3 with a small amount of pantopaque was injected into the cyst in 1 patient in this group who previously had benefited by aspiration of the cyst contents (Fig. 6). A surface dose of approximately 6,000 rads was planned for delivery on the basis of the estimated volume of the cyst. Unfortunately, this individual died on the third postoperative day as a result of an intraventricular hemorrhage caused by laceration of a vein during the passage of the needle. Peripheral blood and cerebral spinal fluid samples taken at frequent intervals after instillation of the isotope indicated that no radioactive material had escaped from the cyst. Figure 7 shows photomicrographs of sections of the wall of the craniopharyngioma removed at



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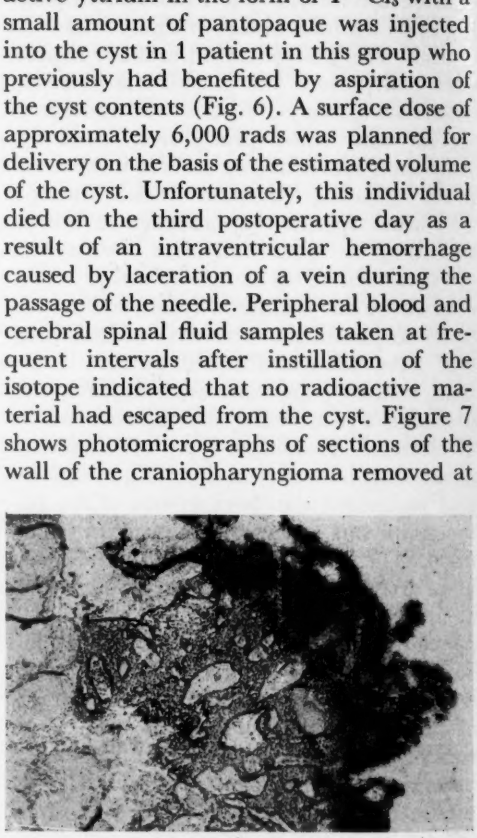

b

FIG. 7. a, Photomicrograph of a radioautograph showing Y^{90} Cl_3 attached to tissue on the internal surface of a cystic craniopharyngioma. b, Y^{90} Cl_3 attached to the surface of the same cyst. Hematoxylin and eosin, ×52.

autopsy. A radioautograph, a, and a standard histologic preparation, b, show the colloidal suspension attached to the tissues. These illustrations demonstrate the manner in which beta radiation can be delivered to the walls of the lesion. The effectiveness of this form of treatment is limited to the depth of penetration of tissue by the beta particles of the particular isotope employed. Structures beyond this range will not be affected. By virtue of this physical factor, it is possible to impart localized doses of radiation at levels which would not be tolerated by the organism as a whole if delivered by roentgen irradiation. It is believed that this form of treatment may prove useful in shrinking recurrent cysts that arise in craniopharyngiomas. Y^{90} has the advantage of greater depth of tissue penetration than Au^{198} or P^{32} in that the maximum energy of the former's beta particles is 2.18 million electron volts as compared with those of the latter isotopes, 0.97 and 1.7 million electron volts, respectively.

This survey of 73 records shows that, as a rule, the individuals with solid tumors and minimal cyst formation did poorly compared with those whose signs developed in conjunction with expansion of a cyst that was resectable or accessible for evacuation by aspiration or open drainage into the ventricular system. Since the ideal of complete surgical removal cannot always be achieved, compromising methods must be employed until better means of dealing with tumors are devised. It is possible that locally instilled sources of beta particles will have more to offer than roentgen irradiation when it is not possible to effect complete extirpation of the lesion.

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STUDIES IN VISCERAL ARTERIOGRAPHY

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AFTER THE DESCRIPTION of retrograde aortography by Farinas in 1941, considerable interest has been directed toward this method of angiography. Odman (10), using Seldinger's technique of percutaneous retrograde femoral aortography, demonstrated high contrast visualization of the aortic segments and their branches by accurate placement of the catheter under fluoroscopic control. Others have introduced refinements to the technique and demonstrated its value as a diagnostic procedure.

This investigation was undertaken in order to identify the hepatic artery and its branches by aortography in the dog. This was done postoperatively in order to verify the ligation of this vessel, which had been accomplished at an earlier stage, and to demonstrate any collateral circulation that had developed. While doing so, it became obvious that other aortic branches could be easily outlined selectively. Moreover, in view of recent reports in the literature of correctable arterial defects, it was believed that this method could be of extreme value in the preoperative identification of such defects in humans.

METHOD

Male and female mongrel dogs weighing 11 to 26 kilograms were anesthetized with intravenous pentobarbital sodium. After a femoral arterial cut-down was performed, a suitable catheter was advanced into the aorta. A slow infusion of heparinized saline through the catheter assured its continued patency. Either a standard cardiac catheter or polyethylene tubing is suitable for femoral catheterization. In this series, Nos. 9 and 10 French catheters and PE240 and PE280 tubing were used. Cardiac catheters are radiopaque to facilitate their subsequent localization within the abdomen. The relatively large internal diameter of the polyethylene tubing, however, permits a more rapid injection of contrast medium. This results in the more consistent production of high contrast arteriograms. A slow infusion of contrast medium through the radiolucent polyethylene tubing, at the proper time, permits its localization. The catheter tip was positioned by means of roentgenography at a point 0.9 centimeter below the superior margin of the first lumbar vertebral body. This point had been previously determined by a study of postmortem specimens to represent the average location of the celiac artery. Using a hand operated pressure injector, 30 milliliters of 50 per cent hypaque sodium were delivered in 2 to 3 seconds. When 75 per cent of the medium had been injected, a Potter-Bucky film was automatically taken by means of a relay switch (8) on the injecting apparatus. The right posterior oblique position was used because it permitted visualization of the entire hepatic artery.

RESULTS

In 28 arteriograms on 18 dogs, visualization of the hepatic artery and its branches has been consistently obtained in all cases (Figs. 1 and 2). The superior mesenteric artery was also well visualized although no attempt was made to place the catheter at this vessel's orifice (Fig. 3). The site of ligation of the hepatic artery was readily identifiable by this angiographic method (Fig. 4). There was no associated morbidity or mortality in this series.

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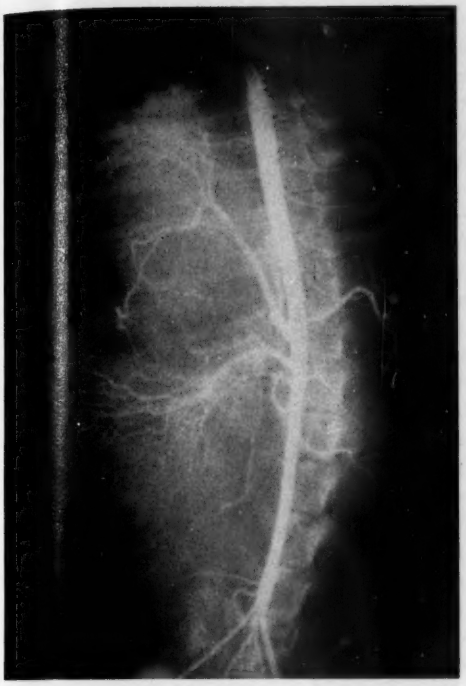

FIG. 1. Retrograde aortogram of dog with experimental ascites. Note simultaneous visualization of the visceral aortic branches with the catheter tip at the orifice of the celiac axis.

FIG. 2. Retrograde aortogram of normal dog. There is good visualization of the hepatic artery and its branches, and this particular timing has produced a high contrast nephrogram.

DISCUSSION

High contrast visualization of the celiac and superior mesenteric arteries is readily accomplished in the dog. The retrograde femoral approach is particularly well adapted to this animal as the artery is easily exposed and admits a large caliber catheter. Collateral circulation about the femoral artery is adequate and no arterial insufficiency has been noted after ligation in this series.

In order to obtain a high concentration of the contrast medium within the aorta and its branches, delivery from the syringe must be rapid. In this series, a flow rate of approximately 15 milliliters per second was found to give optimal results. A film taken ½ to 1 second after the beginning of injection produced good visualization of only the aorta and its main branches. Since this injection rate must be maintained long enough for the contrast medium to reach the small tributaries, 20 to 30 milliliters of medium are required in single film techniques. If a rapid cassette changing device is available, then a 10 milliliter bolus could be delivered and the arterial path traced by taking multiple films.

Techniques which involve advancement of the catheter into individual aortic branches produce the ultimate in high contrast visualization while utilizing small amounts of contrast medium. These procedures, however, involve considerable individual experience and, also, significant amounts of radiation to the patient and operator. This investigation has demonstrated that selective visualization of the visceral aortic branches can be obtained by placement of the intra-aortic catheter adjacent to the branch orifice. A prerequisite

FIG. 3. Retrograde aortogram of normal dog. The catheter tip is at the level of the celiac axis and good delineation of its branches is obtained. The superior mesenteric artery is also well visualized.

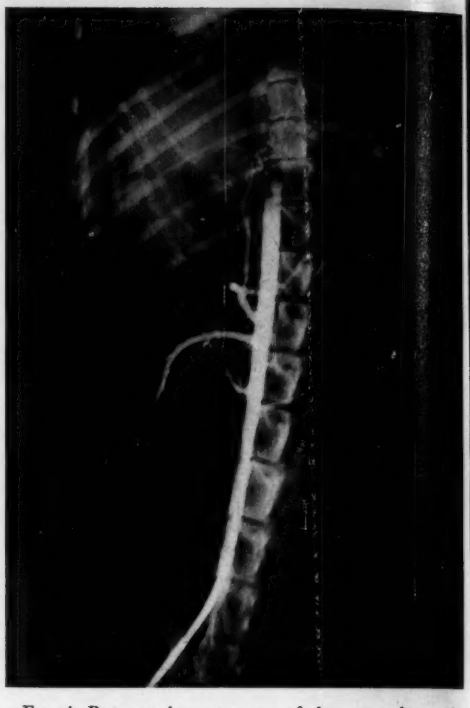

FIG. 4. Retrograde aortogram of dog several months after hepatic artery ligation near the celiac axis. The site of ligation is well demonstrated and is pointed out by the arrow.

for success is retrograde delivery of the contrast medium. A bolus of medium, when forced cephalad against the aortic current, localized for a longer period in the vicinity of the catheter tip than when delivered from above. Much of the bolus, assisted by the elastic recoil of the aorta, is forced laterally into the adjacent branches. Relating the image of the intra-aortic catheter to a fixed point on the lumbar vertebral column has provided a reliable method for positioning the catheter. In no case has the catheter tip been more than 1 centimeter from the intended vascular orifice, placing the latter within the limits of the expanding bolus of contrast medium. The proximity of the aorta to the vertebral column has minimized the error due to parallax.

Hypaque sodium was chosen for this study because of the low incidence of toxic manifestation associated with its use. McAfee has shown that damage to the kidney and spinal cord comprise over 50 per cent of the serious complications attending the use of contrast material in abdominal aortography. In a comparative study of the nephrotoxicity and neurotoxicity of 70 per cent urokon sodium and 90 per cent hypaque sodium in dogs, recently undertaken by Killen and his group, the relative safety of hypaque soduim was well demonstrated. This conclusion was supported in our series in which no reaction to the contrast medium occurred although large amounts were used. When repetition of the procedure was necessary, as much as 90 milliliters of 50 per cent hypaque sodium were administered within 30 minutes.

The clinical use of retrograde arteriography is well established; however, its application to the aortic visceral branches has not been intensive. Helmsworth and his associates used this method of arteriography in the diagnosis of aneurysm of the thoracic and abdominal aorta, as well as in coarctation and cerebrovascular defects. The retrograde approach to aortography has been most severely criticized in its application to obstructive disease. Since the catheter must be passed through the pathologic segment, there is danger of dislodging a bit of atheromatous or thrombotic material which could produce distal embolism. The method has been equally criticized when utilized to demonstrate unilateral iliac arterial occlusion, since disease of the "normal" iliac artery, which would be used for catheter transit, could not be excluded. Visualization of the main aortic channel and its continuation into the lower extremities need not be accomplished by the retrograde method. Much of the objection to the use of the catheter in these conditions then may be averted by utilizing the brachial artery as a point of entrance of the catheter carrying the contrast medium.

It is in the attempt to visualize the visceral aortic branches that retrograde catheterization should find its greatest usefulness. The ease with which the catheter can be placed at the desired level has been described. The most common diseases of the superior mesenteric artery are thromboembolism and primary thrombosis. Glotzer and his co-workers, in discussing their postmortem findings in mesenteric artery thrombosis, have indicated that 50 per cent of their cases were amenable to operation, had the antemortem diagnosis and site of occlusion been known. The technique of retrograde selective catheterization of the superior mesenteric artery has been recently described by Odman (12). The value of this method in recognizing abnormal arterial anatomy, as well as the detection of colonic parenchymatous lesions, is well presented. Arteriography of the superior mesenteric artery also promises to give useful information in such conditions as aneurysm of the vessel itself, tumor of the small intestine and mesentery, and abnormal rotations of the bowel. Visualization of the celiac artery and its branches opens new diagnostic vistas. Abnormal arterial configurations may lead to the diagnosis of intrahepatic tumors. Browning and his associates described 33 cases of hepatic artery aneurysm in the literature which were diagnosed only at operation. Kirklin and his group were able to demonstrate by percutaneous thoracic aortography an aneurysm of one of the branches of the celiac artery. This was subsequently identified at operation as arising from the hepatic artery and was resected. In a recent monograph, Odman (11) has made an extensive presentation of the value of selective celiac arteriography. The technique is utilized for the diagnosis of hepatic cirrhosis and neoplasms, diseases of the pancreas and retroperitoneal structures, and carcinoma of the stomach.

TABLE I.—RELATIONSHIP BETWEEN VERTEBRAL BODIES AND ORIGIN OF AORTIC BRANCHES IN THE HUMAN

Artery	*Range*	*Mean*	*Range for 85 per cent of cases*
Celiac	UT11 to UL2	UL1	MT12 to DL1–2
Superior mesenteric	MT12 to DL2–3	LL1	UL1 to UL2
Right renal	LT12 to ML4	UL2	LL1 to ML2
Left renal	MT12 to ML4	UL2	LL1 to ML2
Inferior mesenteric	ML2 to LL4	LL3	UL3 to UL4
Aortic bifurcation	ML3 to LL5	LL4	UL4 to UL5

The figures refer to the upper (U), middle (M), and lower (L) portions of the thoracic (T) and lumbar (L) vertebrae. Discs (D) are designated in reference to the vertebral bodies they separate.

The remaining visceral aortic branches are also accessible to a catheter. In lieu of selective catheterization, the contrast medium may be delivered to the area of the vessel orifice. The fixed relationship between the origins of the visceral aortic branches and the vertebral bodies may be utilized for this purpose. In the dissection of 300 consecutive cadavers, Cauldwell and Anson have explicitly demonstrated these relationships which are briefly summarized in Table I. The catheter may be positioned rapidly and with a minimum of trauma to the aorta. This is particularly appreciated in

atheromatous disease of this vessel. It must also be noted that atheromas frequently occur near the origins of the aortic visceral branches, and attempts to catheterize these vessels may produce thromboembolism. It is the avoidance of these dangers which justifies the slightly greater amount of contrast medium required by the technique herein described.

SUMMARY

A simple method for retrograde femoral aortography in the dog with high contrast visualization of the visceral branches is presented. Further application of this technique in the human for the recognition of diseases of the celiac and superior mesenteric arteries is believed to be warranted.

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THE IMPORTANCE OF THE ELECTROENCEPHALOGRAM DURING OPEN CARDIAC SURGERY WITH PARTICULAR REFERENCE TO SUPERIOR VENA CAVAL OBSTRUCTION

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THE ELECTROENCEPHALOGRAPHIC CHANGES which accompany superior vena caval obstruction have been infrequently noted in the past few years, although this problem is ever present in the conduct of open heart operations with cannulation of the great veins. Theye and associates, Hudson, and Scurr have pointed out that superior vena caval obstruction can cause electroencephalographic change, and Brechner and coworkers have presented the case histories of 5 patients in whom this occurred during extracorporeal circulation and in whom relief of the obstruction restored the electroencephalogram to normal.

We present the histories of 6 patients, each of whom represents one aspect of this problem and shows that careful continuous monitoring of the electroencephalogram can show not only when a serious situation has arisen but also how a potentially serious situation may be avoided.

In these patients, multiple bipolar electroencephalograph leads have been used from both sides of the head, recording on a 4-channel Grass model III D electroencephalograph. Needle electrodes were placed symmetrically on both sides over frontal, temporal, parietal, occipital, motor, and premotor areas. It was then possible, by changing selector switches on the encephalograph, to record the potentials from any pair of these 12 electrodes. It was found that two leads from each side gave the best screening data and for this purpose left and right motor, premotor and parieto-occipital leads were used. Additional pairs of leads were observed intermittently.

During extracorporeal circulation, numerous factors are monitored and, in some instances, it is the derangement of one or more of these parameters, taken in conjunction with the electroencephalographic deterioration, which points directly to venous obstruction as the cause of the defect. Arterial and venous oxygen tensions in the pump oxygenator, arterial pressure in the internal mammary artery, and venous pressures in the inferior vena cava of the patient, and the level of the blood in the oxygenating cylinder are likewise observed continuously. Venous pressure in the superior vena cava, however, is not monitored, since the electroencephalogram serves this purpose indirectly.

The case reports presented here are taken from the records of the first 40 patients operated on under general hypothermia with a rotating disc oxygenator for extracorporeal circulation. The electroencephalogram was monitored continuously in every instance, and evidence of venous obstruction was found in 6 cases.

CASE 1. Interventricular septal defect. Within 30 seconds of starting perfusion there was deterioration of the electroencephalogram, manifested by a slowing of frequency and reduction of voltage until the tracing was almost flat, although the perfusion pressure remained at 90 millimeters of mercury. The arterial oxygen tension was 390 millimeters of mercury, venous pressure was 20 millimeters, and the blood level in the cylinder dropped rapidly, indicating loss of

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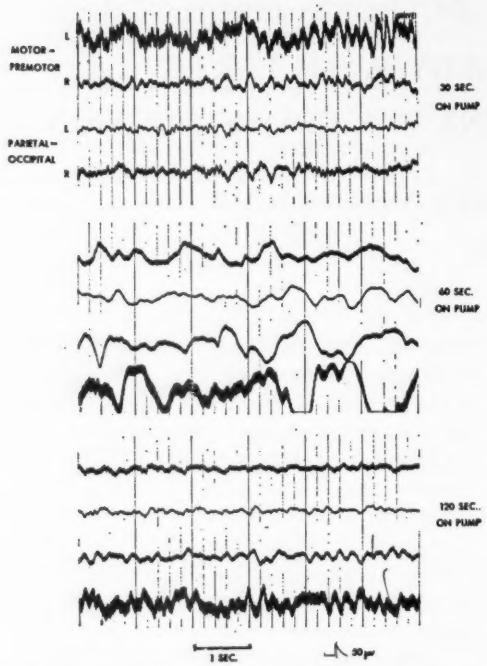

FIG. 1. Case 2. Segments of the electroencephalogram illustrating the rapid deterioration and recovery. Sixty cycle artifact is present in all leads.

blood from pump to patient. Obstruction of the venous line was suspected and the surgeon's attention was directed to it. A kink found in the main venous line was straightened and there was gradual improvement in the electroencephalogram. The pump level returned to normal and the venous pressure fell to 10 millimeters of mercury.

CASE 2. Interventricular septal defect and patent ductus arteriosus. At the start of perfusion, the electroencephalogram showed good activity of mixed 15 to 16 and 4 to 5 cycles per second. After 1 minute of perfusion, there was deterioration of the electroencephalogram from fast frequencies to 2 to 3 cycles per second activity. At the same time, the arterial pressure was 90 to 105 millimeters of mercury, the venous pressure, 15 to 20 millimeters, arterial oxygen tension, 150 millimeters, and the pump level was dropping. A kink was found in the venous line and relief of this kink resulted in rapid reversion of the electroencephalogram to normal and a fall in the venous pressure to 3 millimeters of mercury (Fig. 1).

CASE 3. Tetralogy of Fallot, persistent left superior vena cava. A persistent left superior vena cava was demonstrated preoperatively by angiocardiography. At operation, the decision had to be made whether this vessel was to be cannulated or whether it could be totally occluded during the perfusion. The vessel was therefore dissected out and an umbilical tape was put around it. During a test period of occlusion of the vein lasting 7 minutes, there was progressive deterioration of the electroencephalogram which consisted of the disappearance of 15 to 20 cycles per second activity and emergence of activity at 5 to 6 cycles per second. Within 10 seconds of releasing the tape on the left superior cava, the activity began to return to normal. The anomalous vein was subsequently cannulated through the coronary sinus (Fig. 2).

CASE 4. Tetralogy of Fallot. Three minutes prior to the start of perfusion there was sudden deterioration of the electroencephalogram on the left side. The tracing had shown mixed 20 cycles per second and 6 cycles per second activity, and this gave way to ½ to 2 cycles per second activity. The right side continued unchanged. With the onset of perfusion the record improved very slightly, and the activity on the left side still remained poorer than that on the right. With the cessation of perfusion and the removal of the caval cannulas, the record rapidly returned to normal. The patient recovered without neurologic sequelae (Fig. 3).

CASE 5. Interventricular septal defect. During the insertion of the caval cannulas and before the start of perfusion there was slowing with decreased frequency of the electroencephalogram, which was improved by partial withdrawal of the superior caval cannulas.

CASE 6. Interventricular septal defect, interatrial septal defect, and pulmonic stenosis. The multiple lesions were treated in two steps. During the first period of perfusion the interventricular septal defect and pulmonic stenosis were treated. The pump was then stopped and a few minutes later restarted so the interatrial septal defect could be closed. During the latter procedure there was some operative distortion by retraction of the caval cannulas in the atrium and coincident slowing of the electroencephalographic record on the left side. The venous pressure measured in the inferior vena cava was not elevated, but the record returned to normal when the intra-atrial manipulations were finished.

DISCUSSION

The incidence of superior caval obstruction is relatively high and, as it is a potential hazard, the constant monitoring of the electroencephalogram is considered to be an essential facet in the control of perfusion. The electroencephalographic tracing during extracorporeal circulation has been considered by several authors to be a reliable indication of cerebral well-being, but by this was meant an indication of the adequacy of cerebral oxygenation. Several authors have

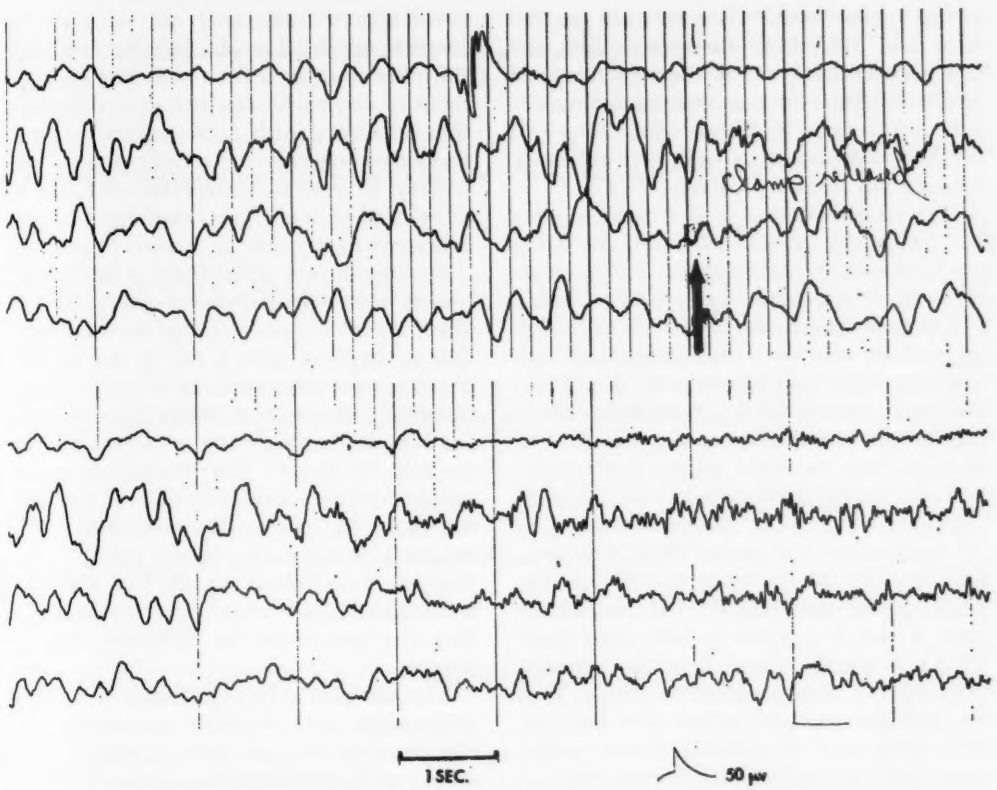

FIG. 2. Case 3. Continuous electroencephalogram showing the rapid recovery after release of the anomalous superior cava. Clamp released at arrow.

mentioned venous obstruction as a cause of deterioration, but this is not an aspect of the subject which has received much attention. Moreover, there is a tendency even to deny the usefulness of monitoring the electroencephalogram during perfusion.

The most common practice in the operating room is for only a single electroencephalographic lead to be monitored, derived from midline or unilateral fronto-occipital electrodes. For many purposes, such as the estimation of the depth of anesthesia, this lead gives sufficient information. However, a single lead may miss contralateral cerebral abnormalities such as were seen in Cases 4 and 6. If the single lead should become abnormal, the presence of the normal opposite side would be missed. In either event, the operator would miss the clue to the correct underlying difficulty.

In the operating room, artifacts of all types are a constant problem to one performing electroencephalography, and, therefore, the use of two leads from each hemisphere gives additional reassurance. The presence of an abnormality in two leads rather than one is added evidence that observed changes are genuine. Perhaps those who deny the value of electroencephalographic monitoring have failed to exploit its full potential.

The cases presented here emphasize the usefulness of the electroencephalogram in detecting cerebral venous obstruction. This may be due to partial or complete occlusion either of the superior cava or its branches or

of the venous outflow line between the patient and the pump. In a way, then, the electroencephalogram is the equivalent of bilateral jugular venous pressure determinations, but, since it detects other causes of cerebral obstruction as well, it is obviously more useful for this purpose.

Venous obstruction of the superior cava can be caused by the caval wall occluding the apertures in the catheter. This is especially likely if venous drainage is by pump rather than by gravity. Occlusion of the left innominate vein by a cannula passing high into the right innominate vein is possible and may account for the occurrence of left-sided electroencephalographic changes. The distance from the right atrium to the junction of the right innominate and left innominate veins in the adult is about 5.0 to 6.5 centimeters and in the child is proportionately less. In an attempt to overcome the possibility of occluding the left innominate vein, a cuffed catheter is now used here. This catheter is passed into the superior vena cava, a tape is tightened around it at the junction at right atrium and superior vena cava, and the catheter is then pulled back until the cuff impinges upon the occluding tape. In this way, only a cuff of tube 0.5 to 1.0 centimeter long actually lies in the superior cava.

The electroencephalogram alone is probably the most sensitive and rapid indicator of the onset of venous obstruction. However, with the added information obtained from the continuous monitoring of arterial and venous pressures and arterial oxygenation, the complete picture is clear-cut. There is an increase in venous pressure, a fall in the level of blood in the oxygenating cylinder, well maintained arterial oxygenation and arterial pressure, and a rapidly deteriorating electroencephalogram. The finding of these changes constitutes a firm indication that the trouble is venous obstruction, and the surgeon should be informed accordingly by the pump team or anesthesiologist so that the site of obstruction may be discovered. If the obstruction involves only the superior caval system there may not be a rise in pressure recorded in the inferior cava, but the other changes will be seen. The development of electroencephalographic deterioration associated with good arterial pressure and adequate cerebral oxygenation is secondary to venous obstruction and not to deterioration in perfusion resulting from the concomitant decrease in venous return.

Several factors other than general anesthetics have been known for a long time to affect the electroencephalogram adversely; that is, hypoxia with a fall in the arterial blood oxygen saturation to 40 per cent, reduction in blood sugar below 50 milligrams per cent, and a severe rise of carbon dioxide content in blood. The electroencephalographic changes seen with each of these are the same, so that electroencephalographic evidence of difficulty cannot reliably distinguish the etiologic agent; but the electroencephalogram does alert the team so that the source of the difficulty can be sought.

The part played by hypoxia can be readily understood, and everyone monitoring the electroencephalogram during perfusion will sooner or later observe an instance of this when, for some reason, the perfusion pressure is unduly low or there is inadequate oxygenation of arterial blood. Most of the original work done on the effects of hypoxia was based on the oxygen saturation of the blood in the internal jugular vein, and the degree of its desaturation was taken to indicate the degree of hypoxia. Under the special circumstances of venous obstruction during extracorporeal circulation, an increase in venous pressure probably results in increased oxygen extraction by the brain and a lowering of the venous oxygen tension. At the same time, there may well be a local rise in carbon dioxide tension, and both of these factors working in conjunction may be responsible for the changes recorded. The changes are rapidly reversible upon relief of the obstruction; and even if the electroencephalogram remains imperfect for periods up to 30 minutes, complete recovery is pos-

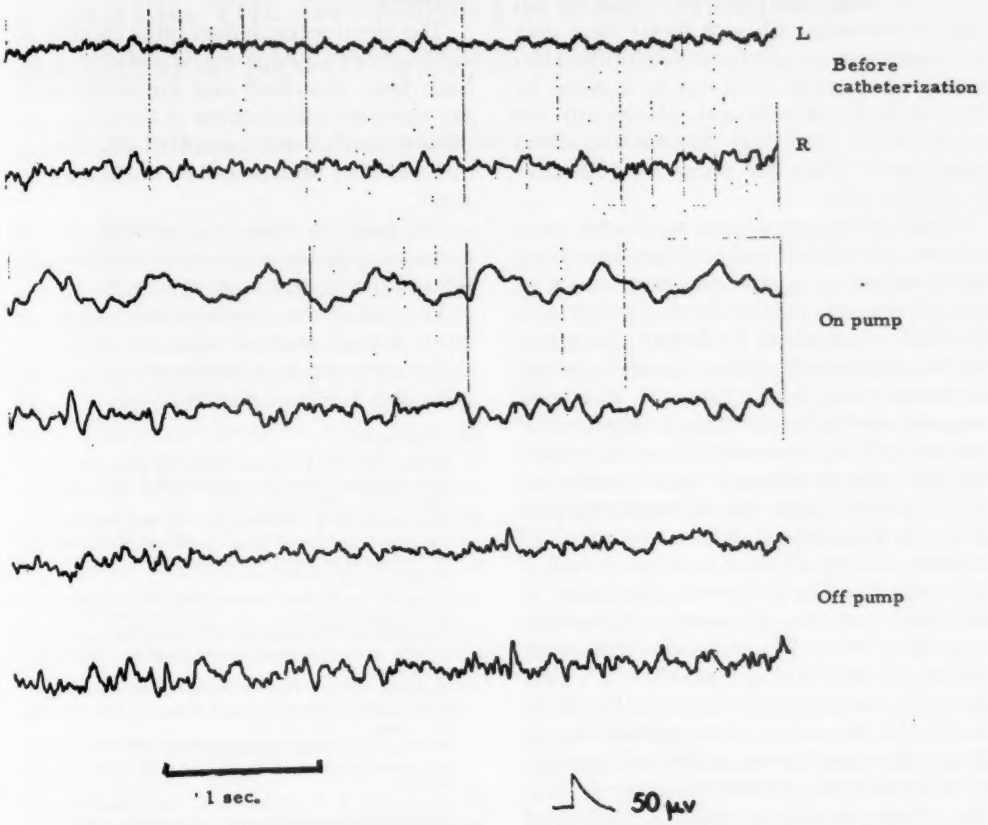

FIG. 3. Case 4. Motor-premotor leads only, due to technical difficulties. Segments of the electroencephalogram illustrate the unilateral deterioration during perfusion.

sible without neurologic or mental sequelae.

Several authors have noticed a temporary deterioration of the electroencephalogram at the inception of perfusion. This has not been our experience, and in only 2 patients whose case histories were not given here has electroencephalographic deterioration developed at the start of perfusion which disappeared after 1 or 2 minutes. In both instances, the only factor that could be found which might account for this transitory change was a low *p*H of the preperfusion blood which was 7.25 in one case and 7.29 in the other. Within 2 minutes of the start of perfusion the *p*H had risen to 7.38 and 7.35, respectively, and the electroencephalogram had improved. Although this is by no means proof of the deleterious effect of a low *p*H on the electroencephalogram, it is perhaps suggestive evidence and should be looked for as an additional factor, especially at the inception of perfusion. Similar changes have been seen by Clowes who gave high concentrations of carbon dioxide to dogs for 15 minutes with resultant electroencephalographic deterioration and subsequent death.

The blood sugar level can seriously influence the electroencephalogram, and this factor may assume considerable importance if the heparinized blood for use in the pump is taken the night before the operation. By the next morning, the glucose level will be

30 to 50 milligrams per cent, and if the patient is perfused with such blood there may be immediate serious flattening of the electroencephalogram. This can be avoided by the addition of sufficient glucose to the pump before perfusion to raise the blood sugar level within the pump by 100 milligrams per cent.

Some of the problems associated with venous cannulation and drainage have been discussed recently, and the importance of cannulation of a persistent left superior cava has been emphasized by Bosher. However, if the collateral circulation through the left innominate vein is adequate, this maneuver may not always be necessary. It is suggested that the left superior vena cava be isolated and occluded temporarily and the effect of this occlusion upon the electroencephalogram be observed. If over a period of 10 minutes no deterioration is noted, then it is believed that the collateral circulation is adequate and the persistent left superior cava may be totally occluded with safety during the perfusion. However, if the electroencephalogram deteriorates, particularly on the left side, this is incontrovertible evidence that cannulation of the left superior cava through the coronary sinus is essential. The advantages of not having a third caval cannulation, if possible, are obvious to the surgeon.

SUMMARY

The electroencephalographic changes resulting from superior vena caval obstruction have been described and the usefulness of the electroencephalogram in detecting such obstruction has been emphasized. Six case histories have been described illustrating this point.

The need for observing multiple electroencephalographic leads, recorded from both sides of the head, has been stressed.

The use of the electroencephalogram to detect the adequacy of collateral circulation in the presence of a persistent left superior vena cava has been described.

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AFFECTING THE DYNAMICS OF BONE HEALING BY ADMINISTRATION OF A BONE EXTRACT

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ALTHOUGH bone fractures are probably the oldest lesions recognized as such in man, and although for years we have known of substances which affect bone growth, there is today no standard therapy used to accelerate the healing of a fracture. The underlying reasons stem from the fact that heretofore quantitative methods have not been available to measure the healing rate in fractures in vivo in the first critical weeks.

It was obviously predictable that as soon as such a quantitative method was available, it would be possible to establish efficacy of substances to accelerate healing. The methods for such studies and the resultant quantitation have been previously reported (2, 3).

This is the first report on one substance used to accelerate the biologic processes involved in healing.

METHODS AND MATERIALS

The methods for assay of the rate of fracture healing are the same as those reported previously (2,3). The substance chosen to test the acceleration of healing was prepared in the following manner.

Cancellous bone was obtained aseptically from young calves and extracted. The materials obtained and tested were mucopolysaccharides which, when examined for their content of nitrogen, uronic acid, hexosamine, and sulfate, and for optical rotation, gave values closely resembling those reported for chondroitin sulfate A and/or C. These lyophilized extracts were sterile, nonpyrogenic, and nonantigenic as evidenced by being immunologically inert in highly discriminating in vivo and in vitro laboratory tests. This substance was chosen because of its reported osteogenic activity in ectopic sites such as the brain.

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White male rats weighing between 200 and 250 grams were used. They were divided into 4 groups of 10 each. Those in group 1 received 0.5 milligram of bone extract in 0.1 cubic centimeter of saline intravenously at the time of the fracture. Those in group 2 served as a control to group 1 and were given 0.1 cubic centimeter of saline intravenously. Rats in group 3 received 4 intravenous injections of 0.5 milligram of bone extract in 0.1 cubic centimeter of saline. The first injection was made at the time of the fracture, the second 2 days later, the third 4 days later, and the fourth on the sixth day. Rats in group 4 served as a control for group 3 and received saline at the same time as group 3. Fractures were induced in the tibia as described earlier (2, 3).

Each animal in each group received 10 microcuries of buffered $Sr^{85}Cl$ subcutaneously at the time of the fracture and 1 microcurie daily thereafter. The 1 microcurie dose was given 30 minutes prior to measurement.

The normal curve of strontium uptake in each control animal and the similar curve of strontium uptake in the fracture of each treated animal were computed as indicated previously (2, 3) by the following formula:

$$\frac{R_{b_f} - R_{b_c}}{R_{b_c}} \times 100$$

in which R_{b_f} is the radioactive count per unit time at the fracture site and R_{b_c} is the same radioactive measurement made at the same site in the identical bone in the control. The standard deviation was between ± 5 to 10 per cent. Thus, all changes greater than ± 5 to 10 per cent are significant.

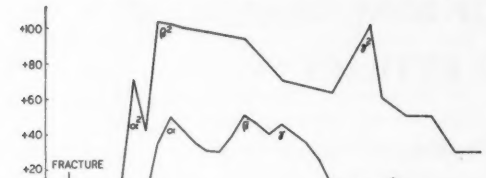

FIG. 1. Curve of dynamics of fracture healing. Each curve represents the mean values of 10 animals. Curve *A* represents the strontium uptake in normal fractures. Curve *D* represents the loss of mineral from other parts of the bony skeleton in untreated animals who have suffered a fracture. Curve *C* represents the radiostrontium uptake at the fracture sites in animals who have been treated with bone extract. Curve *B* represents loss of mineral from other parts of bony skeleton in treated animals.

RESULTS

The bone extract given intravenously in amounts up to 3 milligrams showed no obvious toxic or noxious effects upon the rats.

The effect of the bone extract on mineralization of fractures is shown graphically in Figures 1 and 2. In Figure 1, curve *A* represents the mean value of normal remineralization in the control fractures. Curve *C* demonstrates the difference of values in animals treated with bone extract. These data demonstrate that in the treated animals there is earlier initial uptake of mineral at the fracture site. Furthermore, the amount of uptake at the fracture site in the treated animals is more than twice the control values. In addition, the rate of mineral uptake remains high at the fracture site for some time after the control values have returned to normal. There was no significant effect on the normally observed mineral loss from other bones of the skeleton, as witness curve *D* versus curve *B* in figure 1.

It may be instructive to note the slopes of the control curve versus the curve of the treated animals. It was pointed out previously (3) that in the control group, after the first peak of remineralization (Fig. 1, α), there is inevitably a diminution in mineral uptake. Later there is another peak, β, and a final one on about day 17 designated as γ. These are peaks which are repeatedly seen. They differ in magnitude and constancy from the smaller saw-toothed peaks which would appear in both the control and the experimental curves if each day's measurement had been plotted on the graph. In the experimental curve, three distinct peaks, α^2, β^2, and γ^2, can be seen. They occur at different time intervals than in the control curve, and hence there is no assurance that they represent the same phenomena. However, if α^2 is the same peak as α, it certainly comes earlier in time. The same is true for peak β^2 versus β. In contrast, if γ^2 is a counterpart of γ, it comes later in time. This may be due to the protracted length of the experimental curve. It is certainly of interest that the apparent return of both curves *A* and *B* are similar in time. The same trend is seen in curves *C* and *D*. The somewhat teleologic explanation (3) that the rest of the skeleton contributes mineral while avid uptake of mineral occurs at the fracture site would seem to be reinforced by these data.

In Figure 2 there is the unexpected finding that repeated injections of bone extract do not increase the rate of degree of mineralization to the same extent seen with a single injection but actually seem to depress these accelerated rates.

DISCUSSION

It is rather astonishing that a single injection of bone extract should have such an intense and protracted effect. Further chemical studies will have to be made to establish whether or not the active component is the chondroitin sulfates or whether smaller molecules may be absorbed onto these larger moieties. Irrespective of the specific nature of the molecule, since the substance is injected intravenously, it does not seem likely that it will continue to circulate intact for a prolonged time. The usual fate of such substances is to be phagocytosed, destroyed metabolically, or excreted, depending upon

molecular size and physicochemical structure. Indeed, it is unlikely that the active ingredient in the bone extract would remain in the circulation for more than several hours or, at most, days. Thus, there are two possible hypotheses for the activity of this extract on mineralization of a fracture. The first hypothesis is that adequate amounts of the active factor were absorbed or adsorbed at the fracture site. Subsequently, this factor would remain as a depot source of stimulation of remineralization locally. The second hypothesis is the postulated stimulation of a humoral or cellular system to such an extent that the stimulus would be evident for a matter of weeks. Further exploration with isotopically labeled bone extract derivatives may provide further information as to the fate of the active ingredients.

The observation that multiple injections of the extract did not seem to yield the same magnitude of stimulation to mineralization is puzzling. It might be assumed that a single injection could provide all the stimulus physiologically feasible. If this were the case, it seems unlikely that multiple injections would depress the stimulus. The same reasoning might apply to the hypothesis of stimulation of an endocrine mechanism.

A remaining possibility may lie in the fact that the intravenous injection of so much material can create an unphysiologic situation which can depress cellular responses. It has been noted that the injections of inert bone extract can effect a blockade of the vascular reticuloendothelial system (1). It is conceivable that repeated injections of the extract provide so much inert material for the reticuloendothelial system to dispose of that there is a quasi-blockade of its normal function. Since many of the functions of the reticuloendothelial system are still unknown and since they comprise such a significant proportion of hepatic as well as splenic tissue, a partial blockade of their function may explain the unexpected results of multiple injection of bone extract.

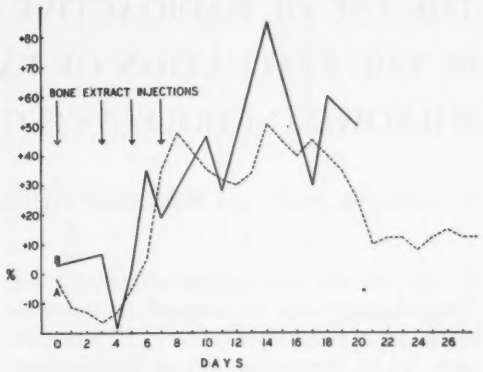

FIG. 2. Curve *A* represents the strontium uptake at the site of a normal fracture as a function of time. Curve *B* represents the uptake of radiostrontium at a fracture site in animals having received multiple bone extract injections and contrasts with Curve *C* seen in Figure 1. Each curve represents the mean values of 10 animals.

In a previous paper (3), it was pointed out that the degree of mineralization is one of the vital processes in the healing of fractures but could not unequivocally be equated per se with the rate of bony union. Thus, further tests of the effect of this bone extract on the strength of union of a fracture must be made to establish this point. However, there seems little question but that this extract does have a stimulatory effect on the physiologic processes controlling remineralization in a fracture.

SUMMARY

1. An extract of bone has been shown to affect the mineralization of fractures.

2. The time(s) of administration of the extract and the amount given appear to play an important role in the total process.

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THE USE OF RADIOACTIVE IODINE LABELED TRIOLEIN IN THE EVALUATION OF FAT ABSORPTION FOLLOWING CHOLECYSTECTOMY

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IN THE DECADE that followed Stanley's and Thannhauser's (5, 6) original descriptions of the use of radioactive iodine (I^{131}) labeled olive oil in the evaluation of fat digestion and absorption in man, numerous clinical and physiologic studies have been presented concerning its use. Results of such studies have been reported in disorders of the pancreas, in cirrhosis, regional enteritis, and ulcerative colitis, and often various types of subtotal gastrectomy, vagotomy, and massive small bowel resection.

The importance of bile in the emulsification, digestion, and absorption of fats is well established. It has been noted that after cholecystectomy, alteration of the composition, concentration, and flow of biliary secretion occurs. The impression is still maintained by many that patients are unable to tolerate fat after cholecystectomy, and that this component of the diet should best be limited. Since, to our knowledge, evaluation of fat absorption after cholecystectomy using I^{131} labeled triolein has not been reported, it seemed of interest to investigate this facet of fat metabolism in such individuals.

In the present article are reported such findings obtained from patients as recently as 7 days and as long as 500 days after gallbladder removal.

MATERIALS AND METHODS

Fat absorption was measured in 131 males and females between 16 and 77 years of age. Group 1, comprised of 28 normal individuals, served as nonoperative controls. Twenty-seven patients in group 2 had undergone operations that did not involve the biliary or gastrointestinal system 7 days prior to the study. In group 3, 22 had been similarly subjected to a variety of surgical procedures 100 to 500 days previous to testing. The 32 patients in group 4 and the 21 in group 5 were subjected to cholecystectomy without exploration of the common ducts 7 and 100 to 500 days, respectively, before this study.

The technique employed for estimation of fat absorption was similar for all individuals. Twelve and 16 hours prior to testing, each individual was given orally 20 drops of Lugol's solution to saturate the thyroid. After a 12 hour fast, a gelatin capsule containing 50 microcuries of I^{131} labeled triolein was placed on the patient's tongue and swallowed with a fatty meal. One-half of the members of each group drank an emulsion consisting of olive oil, 0.5 milliliter per kilogram of body weight, 100 milliliters of milk, 20 drops of Lugol's solution, and 20 milliliters of oily dionosil to opacify the test meal. The other half received an identical meal except that it contained more olive oil—1 milliliter per kilogram of body weight. Some individuals in each group were permitted a fat free breakfast in order to evaluate the effect of feeding, after a test meal, on the blood radioactivity levels. Inasmuch as analysis of the values obtained from the fasted and nonfasted groups disclosed no statistical difference, the data were combined and treated as one. All persons were allowed a fat-free lunch and water ad libitum during the test period.

The progress of the test meal was deter-

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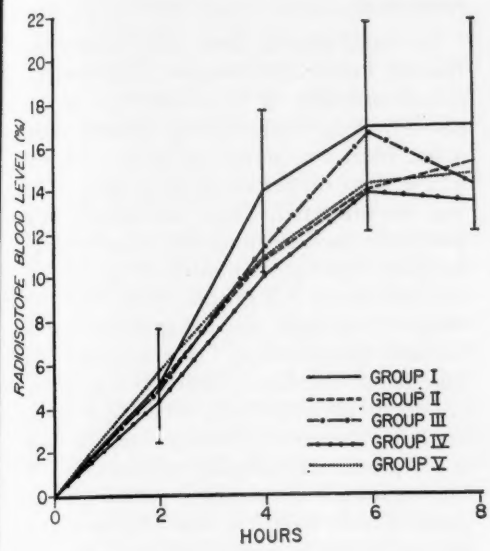

FIG. 1.

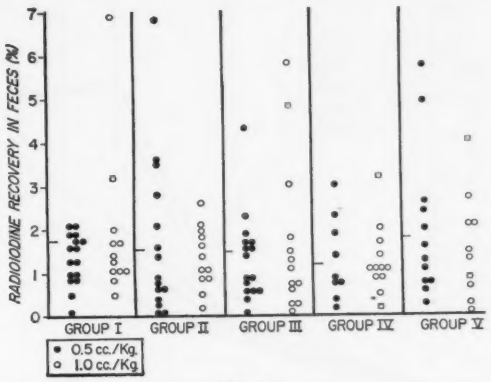

FIG. 2.

FIG. 1. Blood radioactivity levels after test meal with 0.5 milliliter of olive oil per kilogram of body weight. Group 1 represents nonoperative controls with standard deviation at points indicated.

FIG. 2. Total isotope content of 72 hour fecal specimens after test meal. Each symbol represents total collection from 1 individual.

mined roentgenographically 4 hours after its ingestion. Blood samples were drawn at 2, 4, 6, and 8 hour intervals after administration of the emulsion. Radioactivity of these samples was measured in a well type scintillation counter and the radioisotope level of the total blood volume—7 per cent of the body weight—was calculated and expressed as a percentage of ingested I^{131} labeled triolein.

Fecal samples were collected in individual containers for 72 hours subsequent to the test meal. The bottom surface of the sample container was positioned 15 centimeters above a scintillation detector and counted for sufficient time to give statistical accuracy to the data. The gelatin capsule containing 50 microcuries of I^{131} labeled triolein was counted in a similar manner prior to administration to the subject. Direct comparison between these two values permitted the total activity of the 72 hour collection to be expressed as a percentage of the ingested isotope.

All data were subjected to statistical analysis, and a P value of .01 or less was considered significant when comparing any two groups.

RESULTS

Data obtained after ingestion of the fatty meal containing 0.5 milliliter of olive oil per kilogram of body weight are presented in Figure 1. No statistically significant difference in blood radioactivity level was noted between the groups of patients operated on and the nonoperative control group at any sampling interval. Roentgenographic examination revealed total elimination of the test meal from the stomach in all instances by the fourth hour after ingestion. In none of the groups did the mean value of the total radioactivity of the 72 hour fecal collection exceed 2 per cent of the ingested isotope (Fig. 2).

When 1 milliliter of olive oil per kilogram of body weight was used for testing, the results (Fig. 3) demonstrated that those in group 3, operated on 100 to 500 days prior to testing, showed a fat absorption curve similar to that seen for group 1, the nonoperative series. No difference in the pattern of fat absorption was ascertained between group 4 patients who had had cholecystectomy and those in group 2, subjected to other surgical procedures 7 days prior to

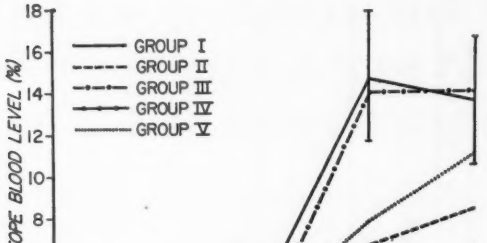

FIG. 3. Blood radioactivity levels after test meal with 1 milliliter of olive oil per kilogram of body weight. Group 1 represents nonoperative controls with standard deviation at points indicated.

testing. When the latter two groups were compared with group 1, both demonstrated at 2 and 4 hours a decrease in absorption approaching significance (P—.05). Six and 8 hour blood radioactivity levels revealed both groups to be significantly lower (P—.01) than the unoperated upon controls. Data obtained from individuals who had had cholecystectomy 100 to 500 days prior to testing (group 5) were found not to be statistically different from those of controls (group 1) except at 6 hours, when an unexplained difference at the 1 per cent level was obtained. Roentgenographic evidence of gastric retention of some of the test meal after 4 hours was uniformly present in all groups. None of the patients in any group exhibited a mean value greater than 2 per cent of the total radioactivity in the 72 hour fecal collection, as is illustrated in Figure 2.

Since no differences were noted after the test meal containing the lesser amount of fat, 0.5 milliliter per kilogram, the data obtained were combined and analyzed according to sex and age. No difference in fat absorption between males and females or in individuals less than and more than 50 years of age was observed (Fig. 4).

DISCUSSION

It would appear from these observations that by 7 days after simple cholecystectomy no abnormality of fat absorption, as indicated by fecal radioactivity, occurred when a test meal containing as much as 1 milliliter of olive oil per kilogram of body weight was administered. Since individuals in the study averaged 69 kilograms of body weight, each received approximately 63 grams of fat. An additional 3.5 grams of fat were contained in the milk, and 7.4 grams in the oily dionosil administered. This amount of fat ingested at one time represents a fat load of considerable magnitude when it is considered that the average normal daily fat intake is 100 grams. The usually recommended test meal contains 0.5 milliliter of oil per kilogram of body weight or less. The finding of a depressed blood radioactivity level in all groups 2 and 4 hours after ingestion of the larger test meal suggested impairment of absorption. This finding is best explained as being due to a decrease in gastric emptying and intestinal motility resulting from the ingestion of the fat. Roentgenographic findings substantiated this fact. By 8 hours the blood radioactivity level was similar in patients in all of the groups receiving the larger test meal except in those recently subjected to operation (groups 2 and 4), in whom the additional effect of surgical trauma, characterized by a more prolonged delay in gastric emptying, was apparent.

Ewald and Boas in 1886 first demonstrated the effect of fat in delaying gastric emptying, and this has been repeatedly substantiated. Further, the effect of surgical trauma on impairment of gastrointestinal motility and the influence of motility on the rate of absorption is well appreciated. It would seem, therefore, that the combined effects of the large fat meal and operative trauma were the factors which delayed the rate of absorption beyond that found in normal controls.

It has been estimated that 10 to 25 per cent of individuals have moderate to severe postoperative symptoms after cholecystec-

tomy for cholelithiasis—the postcholecystectomy syndrome. Although cystic duct remnants, adhesions, common duct injury and stricture, residual stones, continuing pancreatic or hepatic disease, and incorrect preoperative diagnoses have all been implicated, in a certain number of patients no such etiologic factors may be deemed responsible. It was of interest to determine whether such prolonged distress might be related in some instances to faulty fat digestion. In the group of 22 patients having cholecystectomies 100 to 500 days prior to testing, 3 complained of fat intolerance. None of the aforementioned conditions was responsible. No distress occurred after ingestion of the high fat test meal and no patient demonstrated a difference in pattern of absorption from the others. No individual in this study, including those who had cholecystectomy 7 days prior to testing, complained of discomfort after ingestion of either of the test meals.

Analysis of the data obtained from 27 persons 16 to 49 years of age and from 28 patients 50 to 77 years of age revealed no statistical difference in the rate of fat digestion and absorption in either blood or feces. Becker and associates, utilizing chylomicron counts for determination of fat absorption after a fat test meal, reported a definite diminution of absorption of fats by aged people. The chylomicron test, however, has been criticized as having questionable value as a quantitative index of serum lipid changes during fat absorption. Levy, Kraft, and Necheles reported that chylomicron counts represent only discrete fat droplets and that some of the fat globules were beyond the range of demonstration. Turner noticed an increase in plasma lipid activity in old animals after ingestion of I^{131} labeled triolein and oleic acid. These findings were attributed not to an increased absorption but to a diminished rate of disappearance of the absorbed lipid from the plasma. Our findings are similar to those reported by Chinn, Lavik, and Cameron who found no statistical difference in protein digestion and absorption in aged and young persons after a test meal of I^{131} labeled protein.

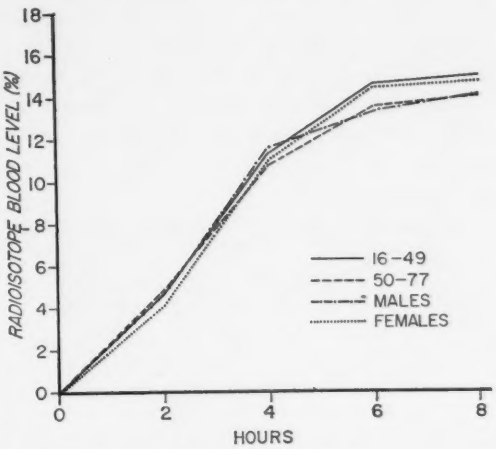

FIG. 4. Blood radioactivity levels after test meal in young and aged persons and in males and females.

SUMMARY

Fat absorption, as determined by blood and fecal radioactivity, was measured in 131 males and females using I^{131} labeled triolein. After ingestion of a test meal containing 0.5 milliliter of olive oil per kilogram of body weight, there was found to be no difference in absorption in: (1) individuals tested as recently as 7 days or as long as 500 days after cholecystectomy; (2) those subjected to operation unrelated to the biliary system; or (3) normal controls.

When the test meal was increased to 1 milliliter of olive oil per kilogram of body weight, a delay in gastric emptying occurred in all groups but, as disclosed by the low 72 hour fecal isotope content, no impairment of absorption resulted.

Not a single individual in this study, including those who had cholecystectomy 7 days prior to testing, complained of discomfort after ingestion of either test meal. Information obtained suggests that the discomfort that follows cholecystectomy—the postcholecystectomy syndrome—is not related to faulty fat absorption. Other etiologic factors must be considered.

Blood radioactivity levels and 72 hour fecal isotope content revealed that the rate of fat digestion and absorption between young or aged individuals and between males and females was not significantly different.

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BENIGN AND MALIGNANT NEURILEMMOMAS OF THE HEAD AND NECK

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NEURILEMMOMAS are relatively rare neoplasms; however, in spite of their rarity, a high proportion of these growths are situated about the head and neck.

Included in this study are the cases in which neurilemmomas occurred above the level of the clavicle in the neck, jaws, scalp, oronasal cavity, oropharyngeal cavity, orbit, and other parts of the head and neck from which surgically removed tissue was available for pathologic study. Tumors which arose in the brachial plexus and presented in the lower cervical region also are included. Tumors of the intracranial portions of the cranial nerves and intraspinal portions of the spinal nerve roots have been excluded.

The surgically excised tissue in all cases was reviewed and only those tumors presenting the established criteria for a benign or malignant neurilemmoma were accepted.

During the period from 1910 through 1957, 148 histologically proved benign neurilemmomas of the head and neck, in 143 patients, were seen at the Mayo Clinic. Five patients had 2 tumors. A total of 16 cases in this group have been reported previously in other studies from the clinic by Bruce, Figi (4, 5), Mayo, New, Penido, Williams, and their associates.

During this same period, 4 patients were seen who had malignant neurilemmomas arising in the head and neck. For the purpose of this study, we elected to make a diagnosis of malignant neurilemmoma according to the precepts of Stout (12) and have discarded all malignant spindle cell tumors unless there was reasonable evidence that they arose from neurilemma cells. One of these cases was previously reported by Penido and associates.

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HISTORY

Neurilemmomas were first established as a pathologic entity in 1910 by Verocay who called them neurinomas. Stout (11, 12) coined the term "neurilemmoma" believing that this tumor arose from the cells of the sheath of Schwann. Among other names employed for this same tumor are Schwannoma, encapsulated neurofibroma, and perineural fibroblastoma.

Neurilemmomas are tumors of the neurilemma or nerve sheath of Schwann and do not arise from the axis cylinders. The characteristic lesion is a solitary encapsulated benign tumor which occurs along the course of a peripheral, cranial, or sympathetic nerve. When the nerve of origin is small, its association with a given tumor may be difficult to demonstrate. On the other hand, if a larger nerve is the site of origin, the nerve fibers are found to be splayed out over the outer aspect of the capsule rather than incorporated within the mass of the tumor. This frequent finding demonstrates the expansile manner of growth of these tumors and explains why the function of the nerve frequently is not impaired until the tumor has obtained considerable size. The small tumors are usually solid but the larger tumors, which rarely exceed a size greater than 10 centimeters in diameter, often exhibit spontaneous degeneration and hemorrhage. All tumors are encapsulated, and the cut surface of the tumor varies from a homogenous solid gray-white to a mottled red to yellow or tan color, with or without cystic spaces (Fig. 1).

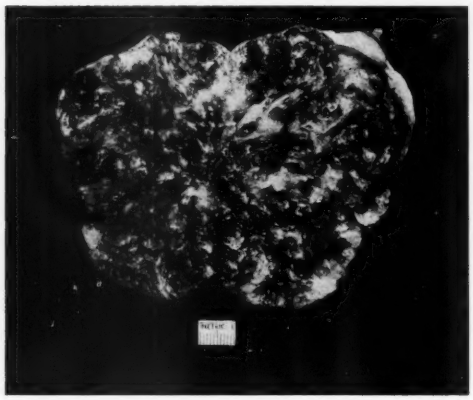


FIG. 1. Section of gross specimen of neurilemmoma which was removed from the pharynx and the cervical region.

Histologically, the tumor may exhibit two distinct patterns usually rather sharply defined one from the other. The one pattern, seen oftener in the solid portions of the tumor than in other parts, consists of delicate spindle cells (Schwann cells) arranged in twisted bands or cords and accompanied by delicate connective tissue (reticulin) fibers. The nuclei often tend to be aligned in orderly rows, called "palisading," with intervening spaces without nuclei (Verocay bodies) (Fig. 2). The second pattern presents a picture of loosely arranged Schwann cells set in a meshwork composed of microcysts and reticular fibers. The degeneration in this myxomatous-appearing tissue is a serous type, no mucin, hyaluronic acid, or epithelium being present. Coalescence of the microcysts produces grossly visible cavities. Hemosiderin and fat laden macrophages are observed frequently in the degenerating portions of the tumor.

The first pattern mentioned often is referred to as the Antoni type I(A) tumor and the second as the Antoni type II(B) tumor. This designation is of academic interest only, since varying proportions of the two types are almost always found in a given tumor.

The size of these tumors is variable, and in our group ranged from 0.3 centimeter in diameter to 10 by 9.5 by 5.5 centimeters.

As mentioned previously, neurilemmomas are seen most frequently about the head and neck. Gore and associates reported that in their study 52 (37.6 per cent) of 138 neurilemmomas located outside the central nervous system were situated in the head and neck. Four of these 52 neurilemmonas were in the parapharyngeal region. Ehrlich and Martin reported the study of 10 neurilemmomas of the head and neck during a 6 year period, 1936 to 1942.

Gore and associates stated that most parapharyngeal neurilemmomas arise from the vagus or cervical sympathetic nerves. Cranmer stated that they may arise from the last 4 cranial nerves or from the sympathetic or parasympathetic nerves. These tumors then expand into the retropharyngeal space and may tend to fuse with the paravertebral musculature. Actually, at the time of cervical exploration, it may be difficult to determine the exact site of origin of these tumors, if the tumor presents in the lateral part of the neck, as well as in the posterior lateral pharyngeal region. Therefore, the designation "parapharyngeal neurilemmoma" becomes somewhat arbitrary and would appear to be rather rare, although 16 of the tumors in our series were considered to belong to this group. In 1956, Gore and co-workers found reports of 47 parapharyngeal neurilemmomas in the literature and added 4 cases. Cranmer has recently reported an additional case.

Ehrlich and Martin, in 1943, questioned the advisability of treatment of large pharyngeal neurilemmomas. They stated that when these tumors are situated in poorly accessible regions, such as the pharynx, surgical removal in certain cases will be attended by a definite risk, especially in older patients. Most neurilemmomas are readily accessible and simple surgical enucleation, if complete, is sufficient; recurrence is not to be expected, even if a portion of the capsule cannot be completely excised. These tumors are resistant to irradiation. Malignant degeneration of a benign neurilemmoma rarely occurs.

DATA IN PRESENT STUDY

The ages of the 143 patients having benign neurilemmomas of the head and neck ranged from 5 to 75 years and the average age was 44.6 years. Sixty patients (42 per cent) were males and 83 (58 per cent) were females.

Neurilemmomas arising in the cervical region. In 77 patients, the neurilemmomas arose from the lateral cervical region. Three of these patients exhibited 2 lesions, thus making a total of 80 tumors. Forty-eight of these patients had definitely known for at least 1 year that they had a tumor, and 21 patients had been aware of a tumor for more than 5 years. One patient was aware of a mass for more than 30 years. In 1 patient, a portion of the tumor extended into the vertebral foramen (dumbbell neurilemmoma) which produced weakness of the left side of the body owing to compression of the cervical portion of the spinal cord.

These tumors, as a group, presented as moderately firm masses of variable size. The dimensions of the largest tumor were 10 by 9.5 by 5.5 centimeters. Roentgenographic examination, when made, is not particularly helpful in establishing the diagnosis, except in the dumbbell type which may demonstrate an enlarged intervertebral foramen. In only 22 tumors could the nerve of origin be determined: 7 stemmed from the sympathetic chain, 7 from the cervical nerves, 5 from the vagus nerve, 1 from the descending hypoglossal nerve, and 2 from the brachial plexus. A total of 5 patients had dumbbell type neurilemmomas, with a cervical portion and an intraspinal portion. Because of the difficulties encountered in removal of these neoplasms by the cervical approach, continued growth of the intraspinal component can be expected unless laminectomy is done to extirpate this portion of the tumor.

With the exception of the 5 complicated tumors which were of the dumbbell type, a recurrence was not experienced by any patient during the following periods of observation: less than 2 years (6 cases), 2 to 5 years (19 cases), and 5 to 10 years (40 cases). Two patients died from other causes

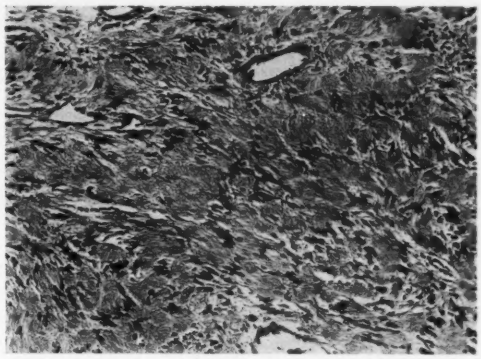


FIG. 2. Section of neurilemmoma showing the palisading of the nuclei which is often seen. Hematoxylin and eosin, × 95.

less than 1 year after diagnosis of the tumor, and 5 patients were not traced.

Included in the differential diagnosis of a soft tissue mass in the neck are malignant lymphoma, lipoma, branchial cleft cyst, chemodectoma, and metastatic malignant cervical adenopathy. Although needle biopsy may be used, our experience with it is limited because, in our opinion, the surgical approach and examination of fresh frozen tissue offer a better chance for correct diagnosis and proper surgical treatment. After adequate surgical exposure, the neurilemmoma can usually be readily enucleated, although there is a real possibility that the nerve of origin will be destroyed unless it is large enough to allow longitudinal splitting of its fibers, followed by simple expression of the mass from the nerve.

Neurilemmomas of the nasal fossa. Five patients were seen with neurilemmomas which arose in the nasal fossa and antral regions. Nasal obstruction was a prominent symptom in 3 patients, epistaxis in 1 patient, and proptosis of the eye in another. The patient reported to have had proptosis when first seen had a tumor that involved the nasal fossa, orbit, and ethmoid region. In 1 patient, the tumor bulged into the nasopharynx and caused deafness in the corresponding ear. In all 5 cases, roentgenographic examination of the sinuses revealed

abnormal opacities in the antrum. The tumors were removed via the Caldwell-Luc or the Denker approach. Two were removed surgically, and in 1 case, radium was used in addition to removal by surgical diathermy. These tumors did not recur and the patients are well. In the other 2 patients, the tumors which were extremely difficult to expose because they were situated in the nasopharynx and the orbitoethmoidal regions respectively, were removed by surgical diathermy, and supplementary radium therapy was given. These 2 tumors did recur, undoubtedly, due to incomplete removal. Since secondary surgical removal, the tumors have not recurred 14 and 16 years, respectively, after removal. In none of these cases was the nerve of origin of the tumor determined.

Intraoral neurilemmomas. Twelve neurilemmomas, all smooth, firm, and mucosal covered lesions, arose from the oral cavity. Five of the 12 tumors were situated in the tongue and were 1.5 centimeters or less in greatest dimension. Four patients had noted a mass for 1 to 15 years and the fifth patient experienced dysphagia for 1 year because of a tumor which was located in the base of the tongue. In none of these patients could the exact nerve of origin be determined. The condition of these patients has been followed for periods of 3 to 18 years, and recurrent tumors have not developed.

In 4 patients, the tumors were located in the floor of the mouth. The masses varied from 1 to 4.5 centimeters in greatest dimension and had been known to be present for from 4 months to as long as 15 years. The nerve of origin could not be determined in these cases. Recurrence has not been noted during the follow-up period of 10 to 19 years.

One neurilemmoma arose in the mandible and 2 in the cheek and region of the upper jaw. In 1 patient, a tumor 5 centimeters in diameter extended into the retromaxillary fossa and a defect in the lateral wall of the antrum was noted upon roentgenographic examination. Simple enucleation of these tumors was sufficient to cure the patients; no recurrence has taken place during the follow-up period of 6 to 18 years. The nerve of origin of these tumors could not be determined.

Neurilemmomas about the face. Thirteen patients had neurilemmomas that arose in the facial regions. These tumors were usually small lesions; however, 1 tumor was 8 centimeters and another 5 centimeters in their greatest diameters. One patient had 2 distinct tumors in the cheek. Most of the tumors were small and soft, and they resembled lipomas or epidermoid cysts. Ten tumors arose in the preauricular region and the cheeks, and 1 each arose in the chin, the upper lip, and the bridge of the nose. No recurrences were noted from 5 to 19 years after simple excision of these tumors.

Parapharyngeal neurilemmomas. Sixteen tumors arose from the parapharyngeal regions. The largest of these tumors was 8.5 centimeters in greatest dimension. In most cases, the tumors presented as smooth, mucosal covered masses bulging into the pharynx in the tonsillar and retrotonsillar region. Additional symptoms in these patients were pain in 5 patients, dysphagia in 2, proptosis in 1, and speech difficulty in 1. One patient had a huge retropharyngeal neurilemmoma that distorted the soft palate and nasopharynx and caused proptosis. The presence of this tumor had been known for 2½ years and it had not responded to irradiation therapy administered elsewhere. Roentgenographic examination revealed extensive erosion of the sphenoid and base of the skull. Exploration of the tumor was attempted, but after the fresh frozen tissue diagnosis of neurilemmoma was made and after consideration of the age of the patient, 72 years, the erosion of the base of skull, and the technical difficulties that would be encountered, an attempt to remove this huge tumor was believed inadvisable. At the time of this writing, 2 years after exploration and biopsy, this patient's condition does not show any change.

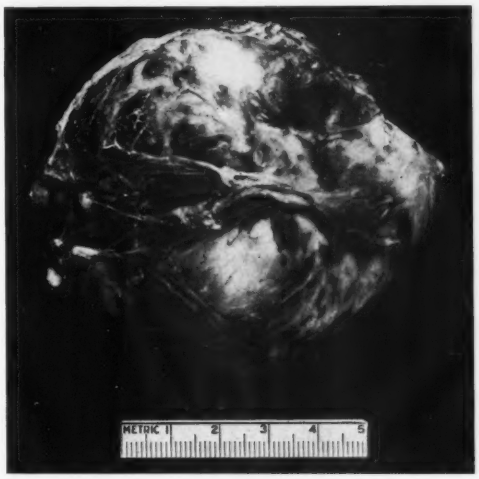
In the remaining 15 cases, the tumors were removed. Five were removed via the cervical

approach, all without incident. The remaining 10 tumors were removed through the mouth, usually after ligation of the homolateral external carotid artery. All 10 were removed readily without incident. One patient who received radium therapy after intraoral enucleation died 4 months later of hemorrhage secondary to a pharyngeal abscess. Ligation of the external carotid artery had been done prior to the intraoral enucleation. Although follow-up data are not available, a second patient in whom the tumor was removed by the intraoral route probably has had a recurrence in the hypopharynx in the 3 years since operation. In only 1 case was the nerve of origin, vagus, determined. No constant relationship of the tumor to the great vessels was noted. One patient had an associated neurilemmoma of the left eighth cranial nerve.

Neurilemmomas arising in the forehead and scalp. Eight patients had neurilemmomas that arose on the forehead or scalp. The largest tumor was 7 centimeters in diameter. Clinically, the tumors resembled lipomas or epidermoid cysts. Pain was not a symptom in these patients. In only 1 patient could the nerve of origin, occipital nerve, be determined. Excision of the neurilemmomas was without incident except in 1 patient. This patient had a neurilemmoma excised from the occipital region in 1923 at the age of 6 years. Recurrent tumors were excised in 1931 and 1941. He has remained free of trouble since.

Neurilemmomas of the orbit (Fig. 3a and b). Seven patients had tumors that arose in the orbit. In all cases, there was displacement of the globe. In 5 cases there was proptosis. In 4 cases, the symptoms had been present for 10 or more years. Pulsation of the globe was absent. In 3 cases, roentgenograms of the orbital region showed erosion of the bony orbital walls. In 3 cases, the tumors were removed via transfrontal craniotomy, and in the remaining 4, they were removed via the anterior approach. The condition of 6 of the 7 patients has been followed up for 7 to 14 years and recurrence has not been reported.

a



b

FIG. 3. a, A large orbital neurilemmoma in a 32 year old patient. The patient had noted proptosis for 20 years. b, Surgically removed tumor.

Neurilemmomas of the middle ear and mastoid. Three neurilemmomas arose in the middle ear and mastoid region. Facial paralysis was present on admission of each of the 3 patients. Loss of hearing and tinnitus were additional symptoms. A tumor was noted upon examination of the middle ear in 1 case. Roentgenographic examination of the patient with a tumor which involved the middle ear revealed evidence of diffuse opacification of the mastoid without destruction of bone. The patient with mastoid involvement showed bony destruction in the mastoid. The tumor was known to have originated from the facial nerve. Removal of these tumors was by radical mastoidectomy. Two patients received supplementary radium therapy.

TABLE I.—FOUR CASES OF MALIGNANT NEURILEMMOMAS OF THE HEAD AND NECK ENCOUNTERED AT MAYO CLINIC, 1910 THROUGH 1957

Case No.	*Sex, Age, yrs.*	*Location of tumor*	*Symptoms*	*Findings on examination*	*Origin of tumor (nerve) and size of mass*	*Treatment*	*Comment*
1	M 50	Left upper cervical	Pain, 2 mos.; mass, 1 mo.	Hard mass	Left vagus; 5 by 2 cm.	Excision, 1935; excision, 1936; x-ray treatment, 1936	Dead 1 yr. after excision; local recurrence
2	F 33	Left supraclavicular	Pain; weakness of arm, 15 mos.	Mass	Brachial plexus (cervical 6-7); 4½ by 2 cm.	Excision, July 1930	Re-excision elsewhere in 1931 and 1932; x-ray therapy; dead 3 yrs. after excision; known local recurrence
3	F 25	Left supraclavicular	Mass, 1 yr.	Mass	Unknown; 4 by 4 cm.	Enucleation	Living 1 yr. after enucleation; untraced thereafter
4	F 46	Left upper cervical	Mass, 2 yrs.	Mass	Unknown; 4 by 2 cm.	Excision	Living 3 yrs. after excision

Laryngeal neurilemmomas. Two patients had neurilemmomas involving the larynx. One patient had a second neurilemmoma in the hypopharynx near the larynx. Hoarseness, stridor, and dysphagia were the symptoms. The smooth, mucosal covered tumor was visualized on mirror examination of the pharynx and larynx. Tomograms of the larynx revealed the exact location of the obstruction in the airway in 1 patient. One tumor was removed by suspension laryngoscopy, while its hypopharyngeal counterpart was removed via lateral pharyngotomy. The other laryngeal tumor was removed by laryngofissure. The condition of these 2 patients has been followed-up for 5 and 6 years, respectively, and the tumors have not recurred.

Malignant neurilemmomas of the head and neck. An elaborate discussion of the histologic details pertaining to the diagnosis of malignant neurilemmoma is not warranted in the scope of this report. It is sufficient to state that at least portions of the removed tissues from all 4 tumors exhibited microscopic evidence of malignancy: increased cellularity, varying degrees of pleomorphism, and easily found mitotic figures, in addition to the recognizable patterns of neurilemmoma. Three tumors did not have a capsule and neoplastic infiltration was recognizable among nerve elements.

Two tumors were considered as of low grade malignancy and were diagnosed as malignant primarily because of cellularity and mitotic figures. More tumors in this category need to be studied in order to assess their activity and inherent potentialities to become locally invasive or to metastasize. Two of the 4 tumors presented more advanced mitotic activity and pleomorphism which left no doubt concerning the malignant potential. Death of the patients having these tumors was caused by the neoplasms 1 and 3 years after the initial attempt to remove them. In none of the 4 cases were there associated stigmas of Recklinghausen's neurofibromatosis.

Two tumors arose in the lower cervical region, and 2 in the upper cervical region. All 4 patients had noted the presence of the tumors and 2 of them had associated pain. The tumors arose in the brachial plexus in 1 of these patients and from the vagus nerve in a second. The nerve of origin was undetermined in the remaining 2 patients. In all 4 patients the tumors were treated by surgical excision. Recurrences in 2 patients were treated by re-excision plus supplementary radiation treatment. Two patients are known to be dead at the time of this study; each had massive local recurrence of the tumor, but it is unknown whether systemic metastatic lesions were present. One patient was living without recurrence 3 years later, and 1 patient could not be traced (Table I). In no

case was there evidence that malignant disease had been precipitated by surgical interference of a previous benign tumor.

COMMENT

We have found that neurilemmomas are usually benign tumors and rarely, if ever, do they undergo malignant change. This is in agreement with Stout (12). In contrast, sarcomas will develop in a small percentage of patients with Recklinghausen's disease.

Neurilemmomas will recur if incompletely removed; however, growth of these neoplasms is usually slow and it may be expedient to take this into consideration in selected cases. Many patients give a definite history of a large tumor present for 10 or more years. These tumors are encapsulated and simple enucleation of the tumor is sufficient. However, simple enucleation without tearing the capsule and leaving a portion of the tumor behind may not always be possible. Pharyngeal neurilemmomas tend to follow fascial and tissue planes between normal neck structures, and thus become lobulated, which makes complete enucleation difficult. In this study, pharyngeal tumors did not recur after primary removal via the external approach. In 1 patient, the tumor was removed transorally and there is a possibility that there has been a recurrence in the hypopharynx. One patient died of massive hemorrhage due to erosion of the great vessels by a pharyngeal abscess. This followed combined transoral removal and radium therapy. Tumors in the neck are usually rather readily enucleated and in our experience recurrences have been rare. Tumors that are near or attached to the prevertebral fascia may actually be a dumbbell type neurilemmoma with a large cervical portion and a more important but smaller intraspinal portion. Unless this possibility is kept in mind in dissecting the tumor free, the presence of an intraspinal portion may be completely overlooked and serious disability or death may result from the slow progression of the intraspinal component.

FIG. 4. Roentgenogram of the mandible in a case of neurilemmoma of the pharyngeal region. This slowly growing tumor had caused pressure erosion of the ascending ramus of the right mandible. This patient was seen recently and is not included in the study.

These tumors exhibit unusually slow growth and, therefore, they will give the same roentgenographic picture of bone absorption that is seen with other slowly expanding lesions, that is, a smooth, radiolucent defect with sharply demarcated borders (Fig. 4), due to gradual resorption of bone. In 5 cases, advanced resorption of bone was present: the walls or rim of the orbit in 3 cases, the mandible in 1 case, and the base of the skull in 1 case.

Because of the large oral incision needed and the difficulties in obtaining adequate exposure, large pharyngeal tumors can be removed best via the external cervical approach. Large pharyngeal neurilemmomas from which specimens for biopsy have been removed transorally present a problem in treatment. These are handled most satisfactorily by waiting until the pharyngeal site from which the specimen was removed has completely healed—usually about 2 months—after which the tumor can be approached externally with little danger of entering the pharynx. Large pharyngeal tumors may require partial parotidectomy, submaxillary

dissection, or sectioning of the mandible to gain adequate exposure of the tumor. We have not found a constant relationship of pharyngeal neurilemmomas to the great vessels of the neck, nor have we found that they have a constant nerve of origin.

Neurilemmomas are resistant to irradiation. At the clinic, irradiation has had little effect on the tumor in cases in which it has been used. Even in regions such as the nasopharynx, where removal of the tumor is anatomically difficult, the use of supplementary irradiation probably is not indicated.

A diagnosis of low grade sarcoma in an encapsulated, soft, yellow tumor that contains areas of necrosis should be viewed with some skepticism. Many benign neurilemmomas are extremely cellular and may suggest malignant involvement. We have encountered a number of cases in which a diagnosis of malignant neurilemmoma has been made previously but in which careful study of the slides has led to a diagnosis of degenerating neurilemmomas. The clinical behavior of the lesions in the ensuing years has substantiated the later judgment. Accurate diagnosis, based on small bits of tissue, such as needle biopsy specimens, is especially difficult.

The majority of neurilemmomas can be removed safely and adequately by surgical procedures. Some authors have reported excellent results in diagnosis from needle aspiration biopsy. Our experience with needle biopsy has not been extensive since we are inclined to prefer direct surgical approach and to rely on fresh frozen sections for an immediate diagnosis. An occasional patient may be better off if the tumor is left alone, especially if it is located in regions of difficult access. One patient in our study had an enormous retropharyngeal tumor; in this case only exploration and biopsy were carried out. This patient was seen 2 years later at which time no change had occurred. In a case of pharyngeal neurilemmoma reported by Ranta, little increase in size of the tumor occurred in the 6 year period after biopsy. Thus, the advisability of removal of some of these enormous tumors should be judged in the light of the patient's age and general condition.

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PREDICTIVE CRITERIA OF PRECLINICAL FEMORAL HERNIA

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THE MOST COMPELLING single factor for improvement in the management of femoral hernia is the continuing high fatality rate of those hernias that become strangulated. This is attributable to its most frequent complication, that of focal mural strangulation of the bowel with subsequent general peritonitis. The combined diagnostic and therapeutic problem of femoral hernia has engaged the attention of many surgeons; notably McNealy, Lichtenstein, and Todd, Hagan and Rhoads, Counseller and Cox, Dunphy, and others. It seems paradoxic that despite striking advances in electrolyte balance, intestinal siphonage, the advent of more potent antibiotics, and improvement of surgical technique in the management of acute intestinal obstruction which is essentially the cause of death in strangulated femoral hernia, the mortality in the disorder has not been altered appreciably during the last 3 or 4 decades.

The incidence of diagnostic error or delay is directly and proportionately related to the fatality rate of strangulated femoral hernia. This parallelism is corroborated by Jarboe and Pratt who reported a 13 per cent mortality in those patients in whom there was a delay of 1 day in diagnosis; after a 4 day procrastination the mortality reached 70 per cent. Such continuing statistical indictments are causing consternation, especially among those surgeons particularly interested in the surgical management of hernias. Dunphy attributes the discouraging prognosis of strangulated femoral hernia to (a) delayed treatment, (b) age, and (c) improper surgical management.

The principle that the earlier and more promptly a diagnosis is made and the more expeditious its treatment the better the results applies with augmented force to femoral hernia. It is proposed that increased emphasis be placed on the diagnostic ingredients of incipient or preclinical femoral hernia. The conception of preclinical diagnosis of femoral hernia is derived from and supported by (1) anatomic, (2) clinical, and (3) cumulative statistical evidence. Moreover, it is the correlative consideration of these basic etiologic and evolutionary principles upon which rests the rationale for the diagnosis of preclinical femoral hernia.

CONDUCIVE ANATOMIC FACTORS

The femoral ring is bounded on three sides by ligaments: the lacunar medially, inguinal anteriorly, and Cooper's posteriorly, respectively. They are generally unyielding and have sharply defined inelastic margins. The fourth or lateral boundary of the ring differs from the others in that it is formed by the femoral vein but with an intervening connective tissue septum which serves to cushion any expansile force due to increased intra-abdominal pressure directed toward this area. A frequent observation is that the medial lacunar ligament (Gimbernat's) may become attenuated and subsequently concave from the same dynamic factors. If, in addition, the fascia transversalis, which is the first barrier to intra-abdominal pressure, has a narrow insertion into the inferior pubic ramus, as has been described by McVay and Anson, it will further expose the femoral ring to undue pressure and in this way contribute to its vulnerability. Under such circumstances, there obtains the potential prerequisites of an incipient femoral hernia by reason of insufficiency of fascia transversalis, an enlarged femoral ring, and an abnormally

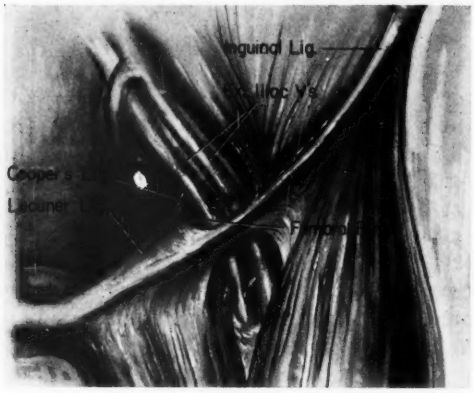

FIG. 1. Anatomy of inguinopectineal region. Normal size femoral ring and fovea with well developed anatomic boundaries.

pliable medial boundary. With these coexisting anatomic findings, the probability of future femoral hernia is much enhanced.

In the center of the femoral ring, there is normally a slight concavity or fovea. The foveal depth is dependent upon the density of the bridging connective tissue strands filling and occluding the femoral canal and perhaps minimally upon the varying intraluminal pressure in the femoral vein. Paucity of the former tissue results in increased patency and interstitial porosity of the canal which lessens its resistance to any focal expulsive force. Continuation of the combined protrusional force with any coexisting anatomic weakness may produce progressive descent of the peritoneal bulb until its subsequent engagement in the accommodating foveal pocket in the femoral canal. Such a protrusion of peritoneum constitutes an incipient femoral hernia which at this early stage of development would not be recognizable clinically. Another dynamic factor is that, directionally, the femoral ring, in contrast to the internal inguinal ring, lies in a horizontal plane. The former ring has no superimposed or surrounding muscular lamina to act as a protective cushion to recurring intra-abdominal pressure thrust upon it. This pressure may attain 100 millimeters of mercury on lifting or straining.

In order to evaluate the dimensional factor of the femoral ring, it was decided that the surgeon performing a Cooper's ligament repair of an inguinal hernia for a patient in whom a femoral hernia is not suspected record the size of the femoral ring and the depth of the fovea. The reason for selecting only Cooper's ligament repairs is that the additive exposure required for this operation affords the opportunity to palpate the femoral ring intrasaccularly and extrasaccularly as well as to visualize it.

These annular and foveal dimensional variants which obtain may be classified into three categories: (1) small ring with shallow fovea (2) intermediate sized ring with deep fovea, and (3) large femoral ring. Those in the first category were promptly excluded as having no potential etiologic role in the development of a femoral hernia. Those falling in the intermediate category, particularly with a recognizable increased foveal concavity (fossa), were considered favorable to the predispositional development of femoral hernia. The third category, large femoral rings, obviously must be placed in the causative class as they are often a precursor to the development of a femoral hernia. Scientifically accurate measurements of the femoral ring, while desirable, were not considered feasible, and the idea was abandoned as not practicable. The criterion of the annular evaluation was based upon whether the tip of the index finger would engage in the ring and whether the floor of the fovea would arrest or permit further advancement of the finger tip. This simple method of measurement was considered sufficiently accurate to be of diagnostic validity by the experienced surgeon who is operating daily.

Before collecting and correlating dimensional data on the femoral ring, attention should be called to several anatomic differences between the femoral ring and the external inguinal ring: (1) The femoral ring is deeply placed in the pelvis which precludes it from external palpation. (2) There is immobility of the femoral ring.

Three of its boundaries are inert and sharply demarcated by resistive ligaments. (3) There is no overlying or circumferential muscular strata to serve as a deterrent to any concentrated protrusional force which might be funnelled toward the femoral ring. (4) The direction of the femoral ring is horizontally placed in contrast to the obliquity of the external inguinal ring. (5) Any informational data on the femoral ring must of necessity be obtained exclusively by anatomic exposure at operation. (6) The intraluminal pressure in the femoral vein is variable. These data were collected on those patients who demonstrated at operation sufficient anatomic but not clinical criteria for a Cooper's ligament repair.

In a series of 103 Cooper's ligament repairs of inguinal hernias there were 19 instances in which the femoral ring or fovea was of sufficient size or depth to permit engagement of the tip of the index finger. This maneuver was preceded by high ligation of the peritoneal sac. With complete exposure of Cooper's ligament there was opportunity by direct visualization to verify the palpatory findings. A femoral ring presenting with these dimensions, although it contained no sacculation, was considered vulnerable and a potential source in the evolutionary development of incipient femoral hernia. Another important and often concomitant collateral finding was the presence of a direct hernia sac. These two coexisting criteria constitute a strong circumstantial chain which was believed to warrant closure or preferably exclusion of the femoral ring. The contention is that operative correction of these potential weaknesses represents a progressive step in the prevention of strangulated femoral hernia. The operative exclusion of a vulnerable femoral ring in the preclinical stage should ultimately result in lowering the over-all fatality rate for femoral hernia by reducing its incidence.

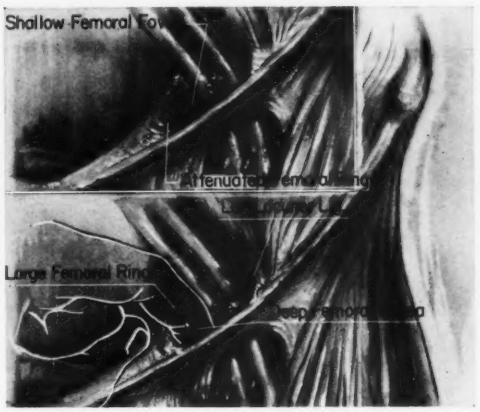

FIG. 2. Variants of femoral ring and fovea. Above, Shallow fovea with dense connective tissue forming its floor and filling the femoral canal. Below, Tip of index finger inserted through femoral ring. When engagement is possible it is abnormal and vulnerable to herniation.

CLINICAL PREDISPOSING FACTORS

The peritoneal infundibulum which is suprajacent to the transitional area of the lateral inguinopectineal region and coincidentally overlies the internal inguinal and femoral rings, respectively, is the source of the femoral hernial sac. Any increased ductility of the overlying peritoneum renders it more susceptible to morphologic changes. Concomitant with its increased pliability, the greater is the likelihood of a peritoneal protrusion entering the femoral ring, especially if augmented by intermittently increased intra-abdominal pressure. The fascia transversalis which is a more resistant stratum surrounds and reinforces the peritoneum. This fascia normally superimposes the femoral ring and is subject to the same focalized expulsive stress as the peritoneum. Anatomically, there is no femoral hiatus in the fascia transversalis; consequently, so long as the fascia transversalis retains its integrity femoral hernia is precluded. Actually, the peritoneum and fascia transversalis may simultaneously, through the process of attenuation, become membranous in consistency which is conducive to the preclinical development of femoral hernia. These strata are in such intimate relationship that when stretched they are almost indistinguishable. For all intents and purposes, they function as a combined structure in their dual descent

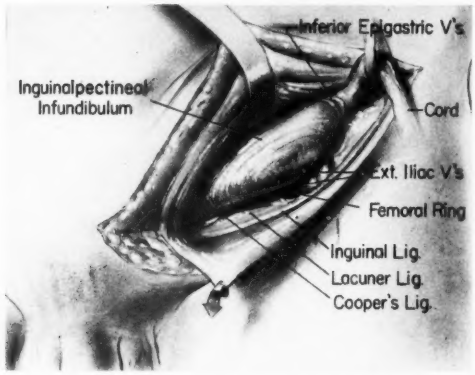

FIG. 3. Normal anatomic boundaries of the peritoneal infundibulum. The fascia transversalis, transversus abdominis, and obliquus internus retracted showing a normal inguinopectineal infundibulum, the most dependent portion of which overlies the femoral ring.

through the femoral ring, comparable to the progressive attenuation of the coverings of the cord in the descent of the testis. Once this preclinical protrusion becomes engaged in a vulnerable femoral ring, it represents the initial step in the evolution of a femoral hernia. In contrast to indirect inguinal hernia, a congenital vaginal process of peritoneum does not occur in the femoral canal.

There has been observed a high sequential incidence of femoral hernias in patients who have had previous inguinal hernia repairs. For instance, McClure and Fallis reported an incidence of 22.3 per cent, Burton 28 per cent, and Fratkin 45 per cent. Despite these incriminating data, it is difficult to conceive of any structural variant created by the different reparative procedures for an inguinal hernia that would predispose to an interligamentous weakness with the subsequent development of a femoral hernia. It seems more logical to assume that the surgeon, in his eagerness to cure the inguinal hernia, concentrates on the congenital sacculation and the deficiencies of the posterior wall of the inguinal canal and does not routinely palpate or visualize the femoral fovea during the inguinal hernia repair. Because of this diagnostic oversight at operation an incipient femoral hernia may be missed. Consequently, no reparative steps are taken at the initial inguinal operation to close or exclude the femoral ring. Moreover, there is clinical confirmation from recorded dimensional findings that some femoral rings are potentially vulnerable.

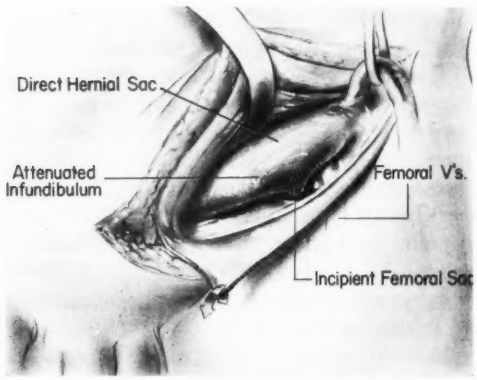

FIG. 4. Combined direct inguinofemoral hernia. The sequence of development of femoral sac from a direct hernial sac. Anatomically, this type of hernia should be designated direct inguinofemoral hernia.

Once an incipient femoral hernia has developed there are no muscular strata immediately adjacent to the femoral area to impede its progress by acting as a sliding valve, sphincter, or operculum in cushioning the intermittent pistoning action of the transfemoral protrusion, as obtains in inguinal hernia. Often in this age group there is fibroplasia and diminished elasticity and tone of the obliquus internus. In effect, there is provided in the circumfemoral area no functional mechanism for augmenting protrusional rebound and thus retarding the progression of an incipient femoral hernia. These significant structural, functional, and dynamic phases, the overlooked operative diagnostic errors, the horizontal plane of the femoral ring, and hypoplasia of the femoral canal septum are all contributing factors which contrive to produce a femoral hernia. Moreover, it seems probable that the rigidity of the ligamentous anatomic boundaries and the direction of the femoral canal account for the higher incidence of strangulation in femoral hernia which, because of

the frequency of obscure clinical findings, carries a tragically higher mortality rate than does the strangulated form of inguinal hernia.

CUMULATIVE STATISTICAL EVIDENCE

The peritoneal sacculations of femoral and direct inguinal hernia arise from the peritoneal infundibulum and are acquired, as opposed to the congenital sacculary patency of indirect inguinal hernia. It is generally recognized that with the aging process there is gradual progressive deterioration in tissue pliability, muscle tone, and fascial elasticity. For instance, at the age of 60, muscles lose 16 per cent of their strength, and there is loss of a half inch in height. Moreover, these degenerative changes have been confirmed by the observations of Krieg on the obliquus internus muscle. He noted that the fascicular component of this muscle, chiefly its minor division, was replaced in varying proportions by fibrous tissue in adults over 40 years of age. Like changes have not been observed in this muscle in babies, children, or young adults during the exposure of this region for hernia repair.

The proneness of femoral hernia to occur in the debilitated and aged increases concomitantly the operative risk. Because of the progressive deteriorating factors, there ensues almost inevitably a higher fatality rate for any corrective procedure. Therefore, it would seem even more compelling to concentrate on the recognition of preclinical femoral hernia a decade or two earlier than when it is generally recognized as manifest hernia. If this diagnostic preclinical proposition were adopted, surgical treatment could be carried out at that period of life in which the risk would be very much less. The principal fault under existing and prevalent methods of treating strangulated femoral hernia is the inordinate delay in making a correct diagnosis in an already debilitated patient. Thus, irreversible complications often develop before the patient reaches surgery.

CONCLUSIONS

1. The diagnostic capacity to predict the development of femoral herniation in some individuals has valid support.

2. There is cumulative evidence that predictive criteria for incipient femoral hernia are recognizable during anatomic exposure for an inguinal hernia repair.

3. The classification of preclinical criteria into anatomic, clinical, and statistical has been described and illustrated.

4. Anatomic variants of the femoral ring and fovea collected from 103 inguinal hernias on whom Cooper's ligament repairs were performed have been submitted.

5. Collateral criteria such as age of the patient, presence of mesenchymal hypoplasia, and the role of chronic intermittent increased intra-abdominal tension should be considered in the over-all evaluation.

6. It is postulated that by the recognition of preclinical femoral hernia it may be possible to reduce the number of manifest femoral hernias and therefore lessen the incidence of strangulated femoral hernia.

7. Femoral hernia is one variant of inguinal hernia. Anatomically, it should be designated inguinofemoral hernia.

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PHYSIOPATHOLOGY OF STRESS INCONTINENCE

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MUCH RESEARCH WORK has been done in an effort to ascertain the defects of the bladder and urethra present in female patients with stress incontinence. Roentgenography, in one form or another, has been the principal tool employed by most of the investigators. Supposed abnormalities observed in patients with stress incontinence include loss of the posterior vesicourethral angle, descent of the bladder outlet, and funnelling of the bladder outlet. Not all investigators, however, agree that these roentgenographic phenomena are found only in patients with stress incontinence; Ardran and associates have observed the same roentgenographic findings in women without obvious stress incontinence. Numerous theories regarding the basic lesion in stress incontinence have been proposed but none has been established as fact. The present status of knowledge concerning stress incontinence has been expressed very aptly by Aldridge in a discussion on normal micturition and stress incontinence. "It seems certain now that stress incontinence is due essentially to abnormalities of structures in and about the vesical neck and proximal end of the urethra. We do not yet have complete knowledge of changes which permit leakage of urine to occur."

In this article it will be demonstrated that the basic defect in most cases of stress incontinence is an abnormally short urethra or primary urinary sphincter when the patient assumes the standing position; and that the appropriate treatment is an operative procedure which prevents the urethra from shortening when the patient gets to her feet.

Before discussing the studies upon which this conclusion is founded, it would be expedient to summarize the present concept of the structure and function of the primary urinary sphincter. Based on a series of experiments performed upon dogs and humans, we (4, 6) have demonstrated that the primary urinary sphincter in both male and female human beings is a tubular structure synonymous with the prostatic and membranous portions of the urethra in the male and with the proximal 3 centimeters of urethra in the female. The structure and function of these tubes are essentially the same in both sexes.

When intravesical pressure is moderate, urinary continence can be maintained solely by the primary urinary sphincter. The primary sphincter shows a resistance which is created by the tonicity of the smooth muscle and elastic tissue in its wall and by its length. In addition, tissue tension created by the fascia and striated muscles immediately surrounding the urethra contributes to the increased resistance observed in the distal two-thirds of the primary sphincter.

When intravesical pressure is elevated to a high level by coughing or straining, the effectiveness of the primary urinary sphincter must be increased to maintain continence; this is accomplished by a two-fold action of the striated pelvic and perineal muscles. The external urethral sphincter and pubococcygeus fibers of the levator ani muscles compress the primary urinary sphincter circumferentially as well as elongate it by pulling it upward or cephalad.

The primary urinary sphincter exhibits its lowest resistance to fluid flow during micturition when urethral length is shortest and tension of the urethral wall against its lumen is least. This situation obtains not only because of relaxation of the striated

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pelvic and perineal muscles but also because contraction of the longitudinal smooth muscle fibers of the detrusor and urethra have shortened and widened the urethra.

During the course of investigations involving the characteristics of the primary urinary sphincter in the female, it was determined that the urethra is an extremely mobile structure whose length varies with type of activity. The lengths of the urethra of 1 normal young, nulliparous, co-operative woman supine and relaxed is 3.8 centimeters; supine with the levator ani muscle contracted, 4.3 centimeters; and standing, 4.3 centimeters.

The length of the urethra in 35 female patients without obvious urinary incontinence and in the supine position varied from 3.0 to 4.5 centimeters with an average of 3.8 centimeters. The urethral length in the standing position varied from 3.0 to 5.0 centimeters with an average of 3.8 centimeters. Note that no continent female had a urethral length of less than 3.0 centimeters in the erect position.

The resistance, in centimeters of water pressure, of various segments of the normal urethra to the retrograde flow of fluid is depicted in Figure 1.

It will be observed that the most proximal and most distal centimeters of the urethra have the least resistance, while the mid 2 centimeters of urethra demonstrate the greatest resistance to fluid flow.

Table I indicates the average intravesical pressures and corresponding intraurethral resistances of the normal female midurethra during varied activities.

After some of the characteristics of the normal female urinary sphincter were determined, experiments were conducted in an effort to identify the basic lesion in women with stress incontinence.

METHODS AND MATERIAL

Twenty-two female patients, ranging in age from 22 to 82 years, were selected as subjects for the first portion of the study. They were part of a large group of patients

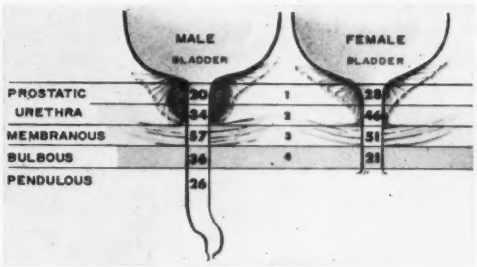

FIG. 1. The resistance of the various segments of the normal male and female urethra to retrograde fluid flow.

with the chief complaint of urinary incontinence. After appropriate studies (5), 22 were considered to have stress incontinence. Nine of the 22 patients had mild to moderate cystoceles or urethrocystoceles at the time of examination. Three of the 13 patients without obvious cystoceles gave a history of having had a vaginal operative procedure for cystocele and associated stress incontinence with no postoperative improvement in the urinary incontinence.

Each patient was subjected to cystometry, urethrometry, cystoscopy, and measurement of urethral length. Although the methods of performing these studies have been reported elsewhere, it is considered of extreme importance to reiterate the method of measuring urethral length. The patient is placed in the lithotomy position and the urethra is catheterized with a No. 18 French retention catheter. This retention catheter differs from the usual one in that it is graduated in centimeters for a distance of 5 centimeters from the balloon. Initially, the centimeter graduations on the catheter were made, but now the catheters can be obtained commercially. After the balloon is inflated with 5 milliliters of fluid, the cath-

TABLE I.—AVERAGE INTRAVESICAL PRESSURES AND INTRAURETHRAL RESISTANCES IN THE NORMAL FEMALE DURING VARIOUS ACTIVITIES

Activity of subject	*Intraurethral resistance of female midurethra, cms.*	*Intravesical pressure, cms.*
Supine	51	17
Supine and straining	70	60
Standing	65	32
Standing and straining	70	85

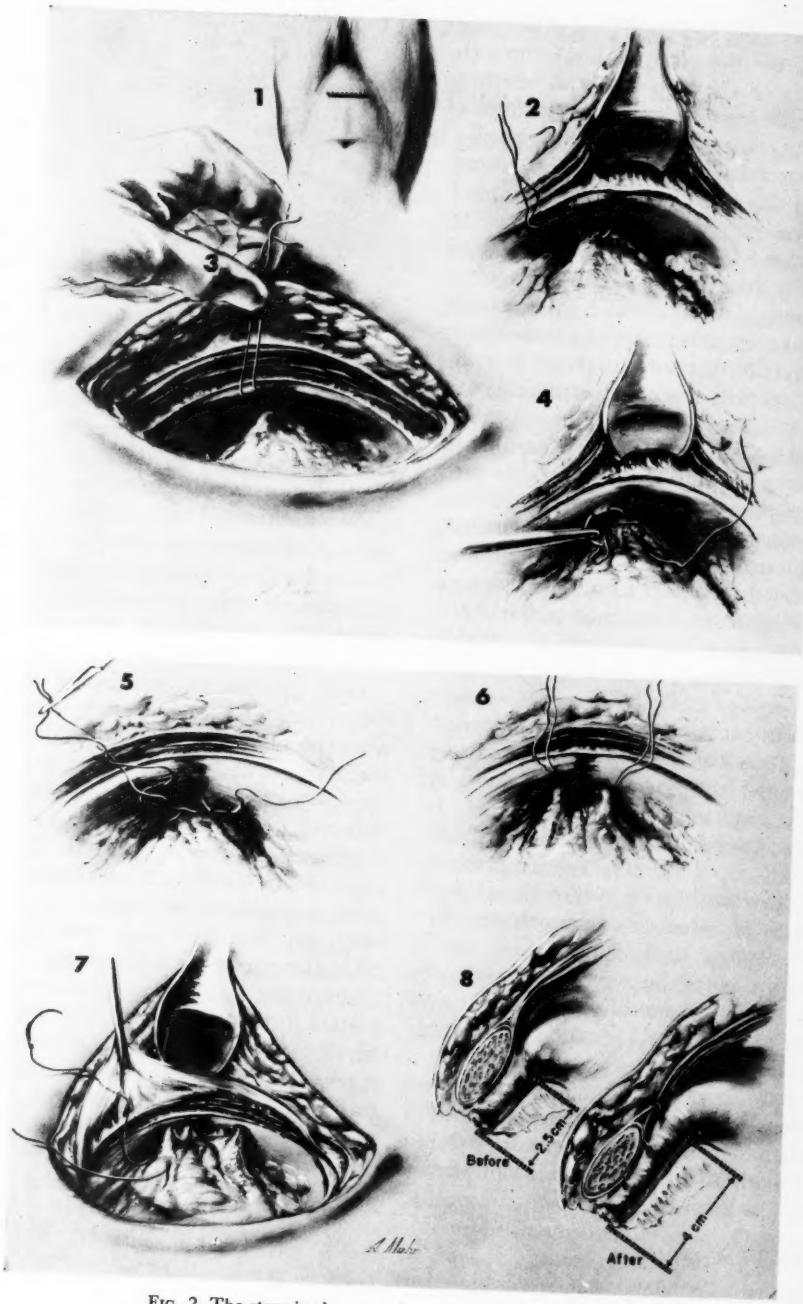

FIG. 2. The steps in the procedure of anterior urethropexy.

eter is pulled gently until the balloon rests against the vesical outlet. The urethral length is determined from the centimeter markings on the catheter. With the catheter still in place, the patient assumes the standing position. The examiner then grasps the catheter with thumb and index finger at the urethral meatus, in order to mark the length, while the nurse deflates the catheter balloon. The catheter is withdrawn from the urethra and the urethral length is determined from the distance intervening between the balloon and the point grasped by the examiner.

Fourteen of the 22 patients, including the 9 with cystoceles and the 3 with previous repair of cystoceles, were subjected to an operative procedure devised by the senior author and designated as anterior urethropexy.

Immediately prior to urethropexy the patient is catheterized with a calibrated retention catheter, the bladder is drained of urine, and the catheter is left inlying. The urethra is approached through a transverse incision made two fingerbreadths above the symphysis pubis (Fig. 2, *1*). After incision of the skin, subcutaneous tissue, and rectus fascia, the recti muscles are retracted laterally to expose the bladder.

The patient is placed in moderate Trendelenburg position in order to move the contents of the peritoneal cavity cephalad and away from the operative field. The periurethral fat is gently wiped from the anterior surface of the urethra so that the urethral wall can be readily identified.

Two parallel rows of interrupted chromic catgut sutures are taken through the anterior wall of the urethra and the overlying symphysis pubis and rectus fascia in order to stretch the urethra and fix it to immobile symphysis and rectus fascia. The technique involves the use of No. 0 chromic catgut suture material and a No. 6 Mayo round point needle. The surgeon mentally divides the anterior urethral surface into two longitudinal halves. The first suture is placed through the most distal portion of the left half of the anterior urethral wall as illustrated in Figure 2, *2*. The suture is taken in a transverse fashion through the entire urethral wall and incorporates about 1 centimeter of tissue in the bite. Before the suture is continued through the periosteum of the symphysis, it is drawn taut and held close to the overlying symphysis in order to judge the place where the suture must be taken so that it will hold the urethra taut (Fig. 2, *3*). The needle is then placed into the periosteum of the desired area and gently pushed and pulled in the arc of the needle through the periosteum (Fig. 2, *4*). The ends of the suture are held while another suture is taken in a similar manner through the most distal portion of the right half of the anterior surface of the urethra (Fig. 2, *5*). Each suture is then tied (Fig. 2, *6*). The next pair of sutures are placed about 1 centimeter proximal and in a manner similar to the first pair. The third pair of sutures are placed 1 centimeter proximal to the second pair; these sutures are usually taken in the region of the vesical outlet and fastened to overlying rectus fascia (Fig. 2, *7*). Figure 2, *8* illustrates a lateral view of the urethra before and after anterior urethropexy.

A Penrose rubber drain is left in the perivesical space and the abdominal wound is closed in an appropriate fashion. The urethral catheter is removed in 4 days and the rubber drain is withdrawn within 24 to 48 hours after the catheter, if there is no unusual drainage.

One patient had been tried on stilbestrol therapy prior to operative intervention. The first 7 patients to be operated upon were subjected to cystometry, urethrometry, and measurement of urethral length 4 to 8 weeks after operation. Only urethral lengths in the standing position were obtained in the remaining 7 patients.

In the third part of the experiment, 1 patient with an extremely large cystocele and without stress incontinence was investigated by endoscopy, cystometry, urethrometry, and measurement of urethral length. After

repair of the cystocele, stress incontinence developed and the patient was again studied. Anterior urethropexy was performed several months after the first operative procedure, and the patient became continent. Repeat urethrometry, cystometry, and measurement of urethral length were performed.

RESULTS

Cystometric examination revealed normal bladders in all of the patients. Two of the 22 patients had atrophic urethral epithelium on urethroscopy; endoscopic examination was normal in the remainder of the patients.

Urethrometry disclosed urethral resistances to be essentially the same as those found in female patients without stress incontinence.

Measurements of urethral length indicated that 21 of the 22 patients had an average length of 2.3 centimeters in the standing position. One patient had a urethral length of 3.0 centimeters, and the remainder varied between 1.8 and 2.7 centimeters.

One woman aged 82 had a urethral length of 4.0 centimeters when in the standing position; this patient was 1 of the 2 found to have atrophic urethral epithelium on endoscopy. Some of the patients had normal urethral length when in the supine position while others had abnormally short urethras. On contraction of the levator ani muscles, some of the patients had increased urethral length; others did not.

Anterior urethropexy alleviated the stress incontinence in all of the patients operated upon, including those with cystoceles. Cystometry and urethrometry findings were not appreciably changed by urethropexy, but urethral length in the erect position was markedly increased. Postoperatively, the urethral lengths in the erect position varied from 3.0 to 5.0 centimeters, with an average length of 3.8 centimeters.

One patient with atrophic urethral epithelium and a urethral length of 2.0 centimeters when in the standing position showed marked improvement in her stress incontinence on estrogen therapy. However, her stress incontinence was not completely relieved until her urethral length was increased to 3.8 centimeters by anterior urethropexy.

The woman aged 82 with atrophic urethral epithelium was not subjected to operation. She was given gradually increasing doses of estrogen in an effort to increase the turgidity of the urethral epithelium. She showed no response to the estrogen even in doses up to 20 milligrams, as evidenced by determination of glycogen content of the vaginal epithelium. Her stress incontinence also did not improve.

Preoperative urethrometric and endoscopic examinations were normal in the patient with the large cystocele. Her urethral length measured 3.0 centimeters when she was lying down and 2.5 centimeters when she was on her feet. Her intravesical pressure was noted to be 12 centimeters in the supine position with a 250 milliliter bladder volume. This pressure was not increased appreciably on exertion or standing. Urinary incontinence could not be elicited on exertion.

After repair of the large cystocele, the patient complained of stress incontinence. Objectively, she demonstrated loss of urine on exertion. Repeat urethrometric, endoscopic, and urethral length studies indicated no changes from the preoperative values. However, intravesical pressure studies now showed that, when the patient stood, the bladder pressure rose to 22 centimeters and that on exertion the intravesical pressure rose to 75 centimeters.

Urethropexy resulted in alleviation of the patient's stress incontinence and increased the length of her urethra when in the standing position to 4.0 centimeters. Cystometric, cystoscopic, and urethrometric studies were unchanged.

DISCUSSION

The experimental observations recorded in this report indicate that the abnormality common to 21 of 22 patients with stress incontinence was an extremely short urethra when the patient assumed the standing position. The average urethral length of the

continent female in the erect position was 3.8 centimeters and the average urethral length of the incontinent female in the standing position was 2.3 centimeters. It would appear that 3.0 centimeters is the critical length in the erect position at which transition from continence to incontinence occurs.

The data suggest, however, that an abnormally short urethra is not invariably associated with stress incontinence and that a urethra of normal length in the erect position is not a guarantee against stress incontinence. Other factors such as intravesical pressure, status of the urethral epithelium, and tonicity of muscle and elastic tissue in the wall of the urethra play a part in determining the effectiveness of the primary urinary sphincter in maintaining urinary continence. Our observations on the patient in whom stress incontinence developed after repair of the cystocele illustrate the role of intravesical pressure in the production of stress incontinence. A high intravesical pressure on exertion cannot develop in a patient with a large cystocele or abdominal hernia, since a high pressure requires a compression of the body cavity by all of the striated muscles surrounding the cavity. If there is a weak spot in the muscular wall of the perineum or abdomen, the pressure will be dissipated by the bulging of the hernia or cystocele. Thus, a patient who is a potential candidate for stress incontinence because her urethra shortens in the erect position may not demonstrate stress incontinence if she has a large cystocele. When the cystocele is repaired, with resultant increase in intravesical pressure on exertion, incontinence makes its appearance.

Indeed, Lund and associates (8) and Hodgekinson have reported that stress incontinence has disappeared in certain women after the development of a large cystocele and also after uterovaginal descensus. It is now apparent that these patients had decreased intravesical pressure which relieved their incontinence. Undoubtedly they would have a return of stress incontinence if the hernial defect were to be repaired.

In our series of cases of stress incontinence 2 patients had atrophic urethral epithelium. One patient had a normal urethral length in the erect position but still was incontinent because of the decreased "tissue turgor" of the superficial epithelium discussed by Aldridge. Thus, in the occasional case, stress incontinence may occur because of atrophic urethral epithelium and in the face of a urethra of normal length in the standing position. Estrogen therapy may improve the stress incontinence if the patient's urethral epithelium responds to the hormone.

Our findings are in accord with the physical law which states that the resistance a tubular structure presents to fluid flow varies directly with the length of the tube. In the normal human female a urethral length of at least 3.0 centimeters in the standing position has been found to be essential for urinary continence under conditions of stress. Abnormal situations which result in a urethral length of less than 3.0 centimeters in the standing position give rise to stress incontinence; and anterior urethropexy lengthens the urethra to 3.0 or more centimeters in the standing position and causes the incontinence to disappear.

It is interesting to note the actual mechanics of the primary urinary sphincter under stress. Ardran and Lund and their associates (7) have demonstrated by roentgenography that when normal females strained or coughed, a "beak" or "infundibulum" of bladder fluid contents entered the proximal third of the urethra and then returned to the bladder after cessation of exertion. Apparently, in normal patients, the urinary sphincter cannot keep the urine confined entirely to the fundus of the bladder when intravesical pressure is increased abruptly. Urine is pushed into the lumen of a portion of the urinary sphincter. It can be readily seen that if the length of the urinary sphincter or urethra is decreased sufficiently, stress incontinence will result, and without necessarily requiring a change in the caliber of the lumen of the sphincter or tonicity of tissue in the urethral wall.

It is quite time that the true relationship between stress incontinence and cystocele, urethrocele, and uterovaginal decensus be established. Abundant evidence in the literature as well as our own data indicates that stress incontinence may occur in individuals without any of the aforementioned lesions. In patients with such lesions as cystoceles and urethroceles, simple anterior urethropexy will abolish stress incontinence without changing the status of the cystocele. In performing the urethropexy, one approximates only the anterior wall of the urethra to the overlying symphysis or rectus fascia; nothing is done to the lateral or posterior walls of the urethra. The concept that it is necessary to buttress the posterior aspect of the urethra is erroneous and should be discarded. In essence, female stress incontinence is due to a lesion of the urinary tract and not the genital tract.

Since the basic lesion in stress incontinence is a shortening, telescoping, or collapse of the urethra on standing, its treatment is to fasten the urethra in the simplest and most certain fashion so that shortening of the urethra does not occur when the patient gets to her feet. This does not mean such unphysiologic, indirect, and uncertain procedures as colporrhaphy, vesicourethrolysis, or fascial slings. The Marshall-Marchetti procedure accomplishes urethral fixation but not in the most physiologic fashion, since sutures are taken unnecessarily through the vagina. This step is not only unnecessary but in common with all the vaginal procedures may cause obstructive uropathy postoperatively by squeezing the urethra between the vaginal wall and the symphysis pubis. Anterior urethropexy fastens the urethra efficiently, rapidly, and without producing postoperative urinary retention.

From the practical viewpoint, a problem of urinary incontinence is approached in the following fashion. After the routine history, physical examination, and urinalysis, the patient is requested to void and then is catheterized with a No. 16 calibrated retention catheter with a 5 milliliter balloon. The catheter balloon is inflated; the urethral length is measured in the supine position; the residual urine is checked; and a cystometric examination is performed. After the bladder is distended to capacity, the patient assumes the standing position with the catheter clamped and still in the bladder, and the urethral length again is measured. After the catheter is removed, the patient is requested to cough or strain, and urinary leakage is observed. The patient is asked to empty her bladder and then reassume the lithotomy position for a second check of residual urine and endoscopic examination of the urethra and bladder. The urethra is carefully scrutinized for defects in the urethral wall and condition of the urethral epithelium. If the patient has no residual urine, a normal cystometric examination, a normal urethroscopic examination, loses urine on stress, and has a urethral length of 3.0 centimeters or less in the erect position, she is a candidate for anterior urethropexy without undergoing any preliminary trial of perineal exercises or estrogen therapy. If the correct diagnosis is made, one can expect 100 per cent of the patients operated upon to be cured of stress incontinence. One must perform all of the examinations advised in order to arrive at the proper diagnosis and avoid pitfalls.

CONCLUSIONS

1. Female stress incontinence is usually due to an abnormal shortening of the urethra or urinary sphincter when the patient assumes the standing position.

2. Stress incontinence is corrected by suturing the anterior wall of the urethra to overlying symphysis pubis and rectus fascia by anterior urethropexy so that the urethra will not shorten when the patient gets to her feet.

3. The phenomena of onset of stress incontinence, with repair of cystocele, and improvement of stress incontinence, with development of procidentia or cystocele, are readily explained by the variations in intravesical pressure on exertion in patients who

demonstrate abnormally short urethras in the erect position.

4. Stress incontinence is strictly a urologic and not a gynecologic entity in that it can occur without any obvious defect of the genital tract and can be completely alleviated by anterior urethropexy in the face of unrelieved procidentia, urethrocele, and cystocele.

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EDITORIAL

ONE SURGEON'S ATTITUDE TOWARD CIGARETTE SMOKING

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A RECENT ARTICLE in *Time* magazine reports that the cancer scare is wearing thin and that the tobacco industry is adjusting accordingly. Apparently the initial impact of the cancer scare was met by widespread promotion of the filter-tip cigarette with its implication that this would afford protection against any possible side effects of smoking. Current sales reports indicate that the consumers' apprehension is definitely on the wane, and that the sales' volume of unfiltered cigarettes is returning to former levels.

The medical controversy over cigarette smoking as the responsible factor in the increasing incidence of lung cancer continues. Those who favor this indictment accept the massive accumulation of statistical data compiled by The American Cancer Society —those who oppose it dismiss those data as pseudoscientific evidence spawned by electronic computers. Experimental efforts to demonstrate the carcinogenic qualities of cigarette combustion products satisfy neither the proponents nor the skeptics. If Koch's postulates are to be fulfilled, experimental animals must learn to smoke—and even if white rats with the hot-cigarette habit should develop cancer of the lung, the question of species sensitivity would inevitably arise. For the moment it appears that a physician's attitude toward smoking remains a conviction that is influenced by his personal habits or his clinical observations.

Whether the relationship between cigarette smoking and the increase in lung cancer will ever be evaluated is a moot point. Nevertheless, excessive smoking cannot be ignored in the everyday practice of medicine and surgery. There are patients who are greatly interested in the doctor's opinions on this subject. This is particularly true in the specialty practices of thoracic surgery, laryngology, and peripheral vascular surgery.

Experience in the field of pulmonary disease has made this surgeon aware of the smoking factor in patients who suffer from severe obstructive emphysema or bronchogenic carcinoma. This conviction is based upon a 12 year period in which the patients' tobacco habits are incorporated in the records as part of the histories. A review of these records suggests that obstructive emphysema is rarely seen in patients who are nonsmokers. The exceptions are usually those few patients in whom obstructive emphysema is associated with extensive parenchymal suppuration, unrelenting perennial asthma, or skeletal deformities of the chest.

Observations relative to smoking in cases of lung cancer are striking, but less obvious than one might believe. One must keep in mind that lung cancer is not a single disease

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entity. There are 5 common variations in cell type alone. Some tumors appear as discrete peripheral lesions, others are multicentric and arise at the bronchiolar or alveolar level, but the majority are encountered in the major bronchi within the hila. Primary lung cancer, like gastrointestinal cancer, covers a variety of individual disease entities with considerable variation in clinical features and prognosis. Hence, to consider a single etiologic factor for the all-encompassing term lung cancer is a gross oversimplification.

No one questions that the incidence of lung cancer has risen steadily since 1920. Pathologists and surgeons are in agreement that the greatest increase has been in cancers of the major bronchi—particularly the squamous cell and the undifferentiated cell types. The overwhelming majority of patients treated by this surgeon for carcinoma of the major bronchi are heavy smokers. This simple observation is derived from the patients' records. Whether or not this is acceptable evidence for scientific appraisal of smoking as an etiologic factor in the rising incidence of lung cancer is of secondary importance. The physician's responsibility is to advise his patients on the basis of established fact—when fact is not established he must follow his convictions and best clinical judgment.

From the standpoint of pulmonary disease it would seem that cigarette smoking is harmful only when it is excessive. Since there is considerable individual variation in smoking habits, the definition itself of excessive smoking raises issues. Every thoracic surgeon listens with weary patience to the heavy smoker's rationalization of his addiction. The smoker's lack of insight is reminiscent of the obese patient's insistence that her diet is barely life-sustaining. The length of the cigarette, the character of its tobacco, the type of paper wrapping, and the presence of a filter, plus the techniques of simple puffing or down deep inhaling are points raised by the "thinking man" who smokes too much. To conserve energy and to avoid unnecessary argument, these points can be dismissed as quibbles, and a simple definition of excessive smoking can be formulated. This definition is predicated on the basic assumption that a persistent cough is never normal; hence, whatever number of cigarettes is required to create a cough habit must be considered excessive for that individual.

In clinic practice a cigarette cough is frequently dignified by the term chemical tracheobronchitis. In simple fact the smoker's cough is a reflection of the underlying chronic irritation that may be attributed to abuse of cigarette smoking. If the cough disappears after a 2 week period of total abstinence from smoking, then the clinical impression has been substantiated by the simplest of all tests. Since the majority of patients with obstructive emphysema and bronchogenic carcinoma admit to years of chronic cough and excessive smoking, it would seem a little odd to discount any possible causal relationship.

In light of the aforementioned observations and impressions, it would seem that the casual smoker who demonstrates little evidence of tracheobronchitis assumes little risk to his health. The smoker who demonstrates a persistent cough, in all probability has a habit stimulated by compulsion, and his consumption of cigarettes should be considered as excessive. This surgeon believes he acts in the best interests of his patients when he cautions those who smoke to heed the warning that is given by the presence of persistent cough.

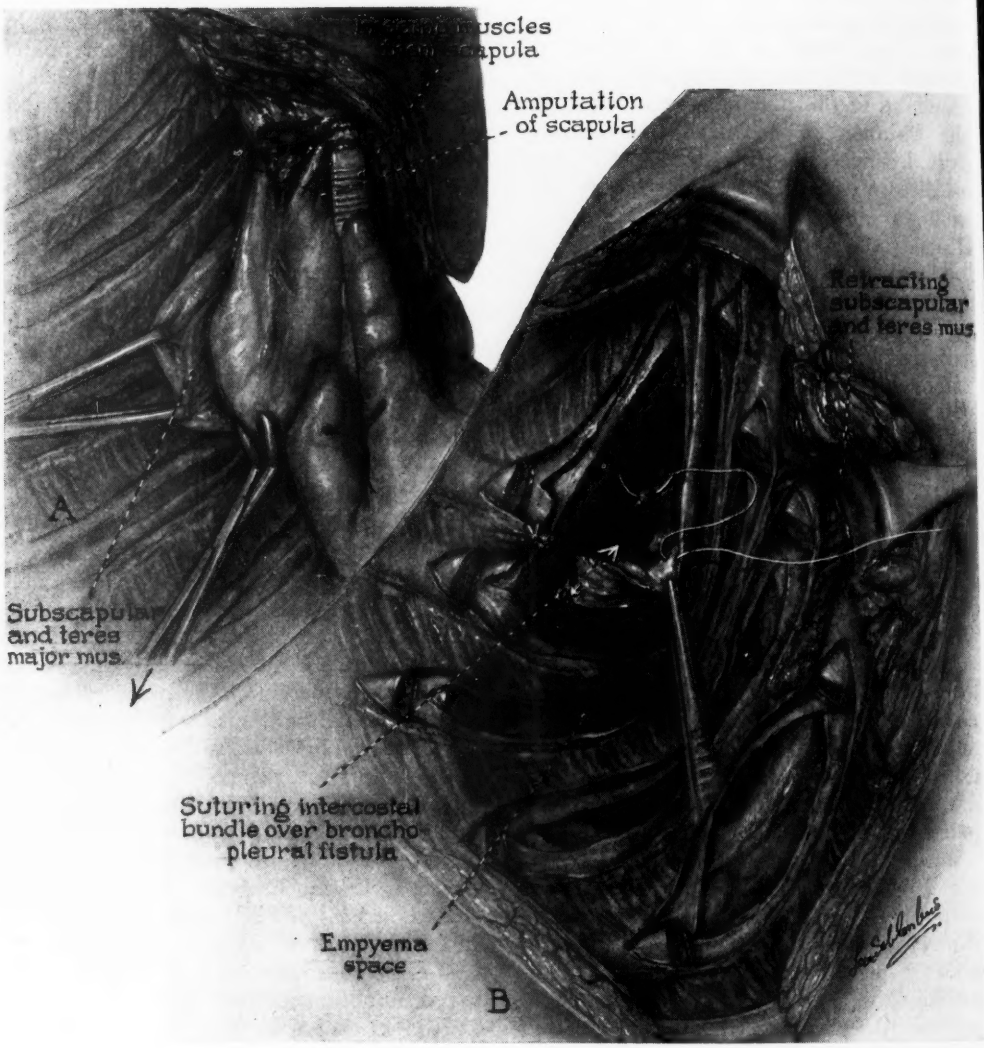

FIG. 3. A, Drawing shows resection of scapula. B, Fistula closure.

Partial Scapulectomy with Subscapular Muscle Flap Operation for Postpneumonectomy Empyema.—Elliott Michelson.

THE SURGEON AT WORK

PARTIAL SCAPULECTOMY WITH SUBSCAPULAR MUSCLE FLAP OPERATION FOR POSTPNEUMONECTOMY EMPYEMA

ELLIOTT MICHELSON, M.D., Baltimore, Maryland

THE SUCCESSFUL TREATMENT of chronic empyema depends upon the closure of all fistulous communications, the removal of all necrotic and infected tissue, and the obliteration of the rigid walled space. The operation of Grow embodies the following principles: it utilizes thoracoplasty to reduce the space, removes the thickened inelastic parietal pleura, uses the pliable intercostal muscles for filling the space and for closure of the fistula, preserves intercostal nerve function, and maintains a rigid chest wall. In postpneumonectomy empyema, the pleural space is large and intercostal muscles are rarely sufficient to obliterate the space. Moreover, if portions of this muscle have been used to close fistulous communications, inadequate tissue remains to cover the thick avascular visceral pleural peel. It is in these instances of postpneumonectomy empyemas that the addition of partial scapulectomy and the subscapular muscle flap succeeds in all criteria of treatment.

Grow indicated that Estlender first proposed thoracoplasty as a method of obliterating the chronic empyema space. Schede realized the inadequacy of this procedure and proposed the removal of the entire overlying parietal empyema wall after rib resection. In this operation the intercostal nerves and periosteum were resected with resultant paresthesias and paradoxic motion of the chest wall. Roberts modified the Schede operation by making a hinge flap of the intercostal muscle and periosteum anteriorly and allowing the flap to fill in the space. No paradoxic motion followed this procedure, but there was marked nerve weakness, the flap was inelastic, and the space was usually not completely obliterated. Heller and Wangensteen contemporaneously preserved the intercostal nerve by maintaining the continuity of the intercostal muscle bundle, but made it somewhat more pliable by incising each periosteal bed, making multiple ribbons which would hang hammock-like over the visceral peel. Grow, in 1946, refined the Wangensteen operation by dissecting the thickened and infected parietal pleura from the intercostoperiosteal mass and left these pliable ribbons of muscle together with its nerve and blood supply to fill the space. The only failure in 13 cases was in a patient in whom empyema developed after pneumonectomy. Kergin, in 1953, described an operation for chronic plural empyema which was quite similar to that of Grow.

The use of a pedicled muscle flap to close a bronchopleural fistula was first described, according to Garlock, by Abrashanoff in 1911. Garlock reported the use of the subscapular muscle as one of the muscle flaps in a multistaged operation for chronic empyema. Robinson suggested the use of the subscapular muscle as a fill but believed scapulectomy to be too mutilating.

Empyema after pneumonectomy with or without bronchopleural fistula is best treated by preliminary tube drainage. After adequate drainage, the empyema space diminishes in size and assumes an S shape with the narrow apex in the paravertebral gutter at about the third intercostal space, the shallow base just above the

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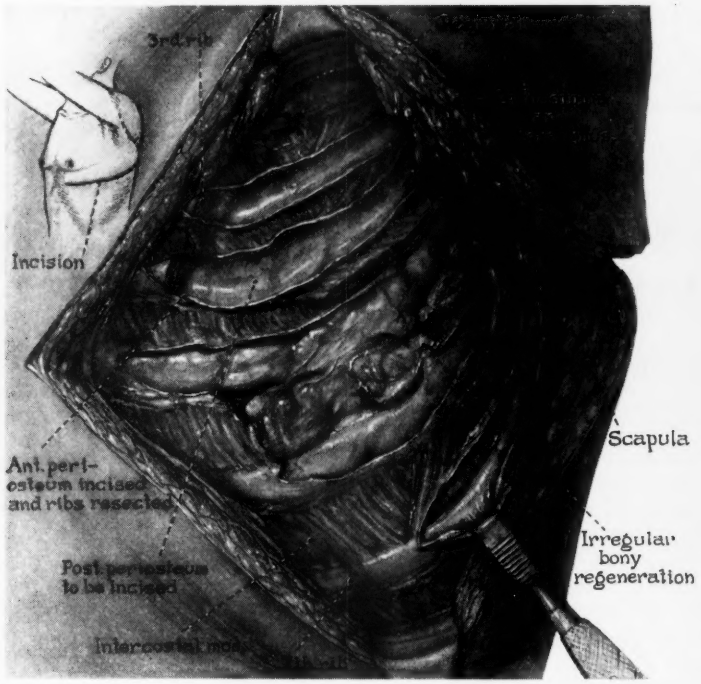

FIG. 1. Drawing demonstrating the resection of the ribs overlying the empyema space.

anterior diaphragm in the fourth or fifth interspace, and its widest diameter at the posterior axillary line. The walls of the cavity become quite thick, covered by granulation tissue and necrotic debris which when curetted leaves a firm white avascular surface. After subperiosteal resection of the segment of ribs directly overlying the empyema space, there is slight decrease in the width of the space; and after incision of the periosteum of the rib bed, the muscle ribbons drop down in hammock fashion to obliterate the central portion, but not the periphery of the space.

By excision of the parietal peel beneath the intercostal muscle and periosteum, the entire empyema space can be covered with soft viable tissue except in the rigid paravertebral area. Then, the angle of the scapulae rides over the first unresected rib below the empyema space. If the scapula is allowed to remain outside the rib, a large dead space remains, and if placed beneath the rib, the scapula is immobilized and shoulder action restricted. By resecting the lower third of the scapula, free motion of the shoulder is allowed and the dead space is obliterated. After this has been accomplished, the lower two-thirds of the subscapular muscle and the teres major muscle can then be used to completely cover the visceral area.

OPERATION

Prior to definitive surgery, all skin irritations due to protracted drainage and the presence of the tube should be cleared. The empyema space may be irrigated with solutions containing proteolytic enzymes such as varidase or tryptar, provided that large bronchopleural fistulas are not present. The patient is placed in the anterolateral position with the arm abducted and elevated. The anterior and lateral portion of the infrascapular scar is incised together with excision of the fistulous tract. The wound is developed through underlying muscle and fascia, and the ribs overlying the empyema space are resected in subperiosteal fashion, with care being taken at areas of irregular bone regeneration that the muscle fibers are not destroyed (Fig. 1). All bleeding points are carefully clamped with

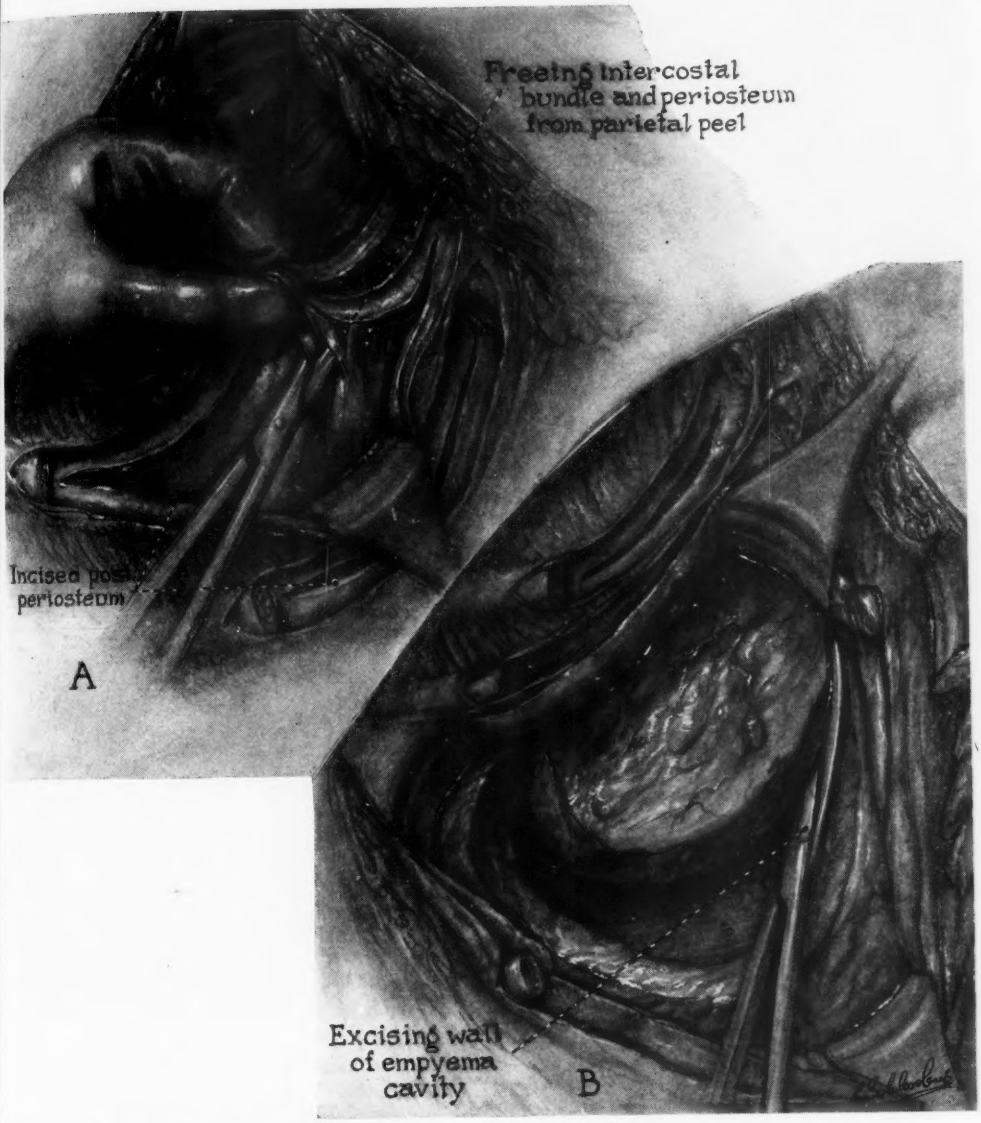

FIG. 2. A, The intercostal muscle bundle is freed from the empyema wall. B, The empyema cavity is unrooted.

fine forceps and cauterized with the Bovie current in order to minimize blood loss and tissue necrosis. The parietal pleural together with the thickened underlying peel is freed from the overlying periosteum and intercostal muscle and then excised (Fig. 2A and B). The plane between the periosteum and pleura may have been obliterated by the previous infection of the chest wall so that care is necessary to preserve the intercostal myoneurovascular bundle. By incising each posterior periosteal bed, ribbons of intercostal muscle together with nerve and blood

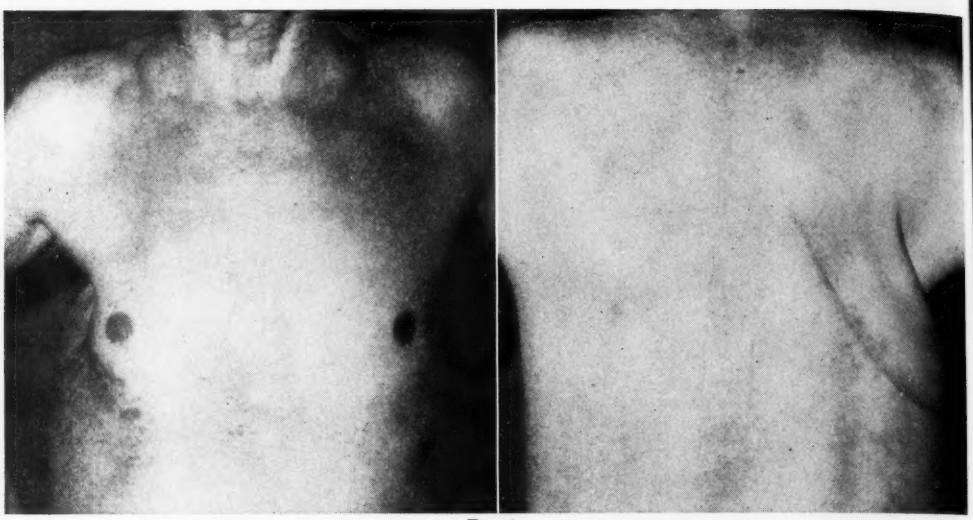

FIG. 4.

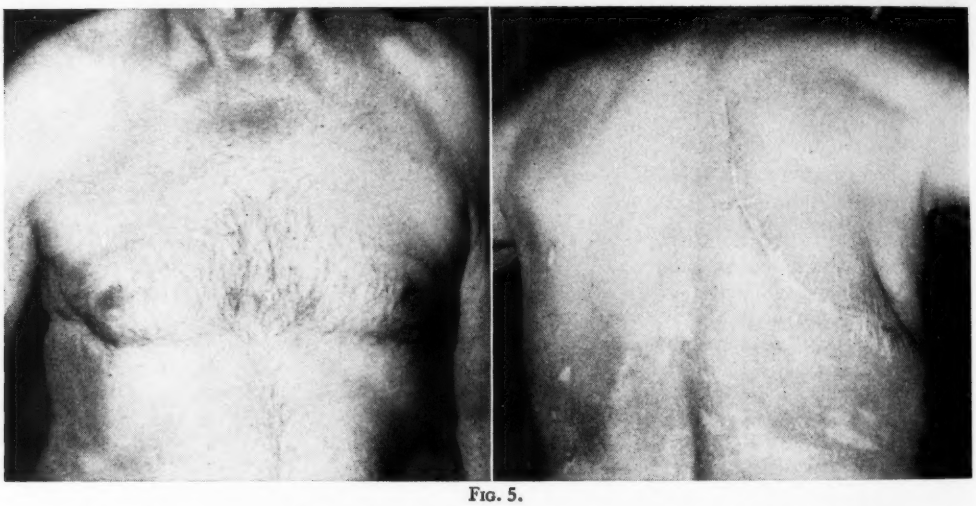

FIG. 5.

FIG. 4. Photographs of patient taken 1 year after operation for empyema and for bronchopleural fistula following pneumonectomy for bronchogenic carcinoma.

FIG. 5. Photographs which were taken 1 year after operation for empyema and bronchopleural fistula which followed pneumonectomy for arteriovenous fistula of the lung.

supply are fashioned. These ribbon muscles can be retracted and the visceral pleura curetted until the surface is white and glistening (Fig. 3B). Any fistula present can then be obliterated by cutting the highest muscle bundle anteriorly and suturing it into or tightly about the fistulous opening (Fig. 3B). If the fistulous opening is too large for one muscle bundle to fill the space, the subscapular muscle mass, which includes the teres major muscle, can subsequently be used to suture directly over the opening. At this point one must determine whether the intercostal muscle bundles will adequately obliterate the space or whether further muscle is necessary to completely cover the visceral pleural wall. If the latter decision is made, the tip of the scapula is

retracted into the wound with a towel clip, incision made along the edge with a sharp knife, the dorsal and ventral muscles freed with a sharp periosteal elevator, and the lower third of the scapula excised (Fig. 3A). Few bleeding points are encountered and the muscles are easily freed.

A large triangular flap which consists of the subscapular and teres major muscles can then be swung forward to fill the empyema space from the paravertebral area to its anterior border. The muscles may be insinuated between the first and second muscle bundles, sutured down over any fistula, and its low angle will fill the space down to the diaphragm (Fig. 6). A small catheter is placed above the muscle at the apex and another catheter placed at the lower angle of the space anteriorly for drainage. Muscle and skin are then opposed with either catgut or steel. The arm is held close to the chest wall in a Velpeau bandage for the first 3 days after operation, and at the end of that time active arm exercises are encouraged.

This operation has been used in 2 cases of empyema which followed pneumonectomy, both of which resulted after severe staphylococcus infection of the chest wall and pleural space. In 1 instance a bronchopleural fistula was present. The lack of definitive endothoracic planes did not allow meticulous separation of the intercostal muscle from the parietal peel. The subscapular muscle mass filled the space, obliterated the fistula, and allowed primary closure of the wound. There was no loss of intercostal nerves and no paradoxic motion followed. Resection of the scapula was not attended by any marked deformity of the chest or spine, and there was little loss of shoulder or arm motion. Figures 4 and 5 show configuration of the chest after surgery.

The limited thoracoplasty of Grow together with partial scalpulectomy and subscapular muscle flap to obliterate the fistula and empyema space will allow primary healing of postpneumonectomy empyema. This method of closure is indicated if the empyema space is great, if large or multiple fistulas are present, and if a prior staphylococcus infection of the chest wall has obliterated the plane of cleavage between the parietal pleural peel and the intercostal muscles. The subscapular and teres major muscles are large enough to fill the empyema space, and the intact nerve and blood supply prevent secondary shrinkage of the muscle mass.

FIG. 6. Empyema space obliterated.

SUMMARY

In large postpneumonectomy empyema cavities the Grow modification of the Schede thoracoplasty may be inadequate because of lack of sufficient muscle mass to completely obliterate the space. By resection of the lower third of the scapula, a large muscle flap consisting of subscapular and teres major muscles becomes available to cover visceral peel and obliterate all fistulous tracts. This procedure has been used in 2 instances and found to be simple and sufficient; it allows primary closure and is attended by no appreciable shoulder disability.

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INTRAVENOUS PLACENTOGRAPHY

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THE ROENTGENOGRAPHIC DEMONSTRATION of the placental site in patients with suspected placenta previa is difficult and frequently inaccurate when performed by conventional methods. It is usually necessary to obtain multiple soft tissue films in different projections. Introduction of contrast material or air into the bladder is sometimes necessary, adding to the discomfort of the patient and the risk of infection.

Several investigators have shown that the placenta can be well demonstrated by direct or retrograde percutaneous aortography. However, these techniques are specialized and are difficult to perform. Romney and co-workers have demonstrated that approximately 500 cubic centimeters of blood per minute or one-eighth of the cardiac output in the pregnant woman at term is diverted to the placenta. Since such a large portion of the circulating blood is diverted to the placenta, it seemed logical that the technique of intravenous opacification of the aorta could be modified to produce visualization of this organ. In this article, the technique and results obtained with intravenous placentography are briefly described.

TECHNIQUE

A No. 15 needle is inserted into the antecubital vein and is tested for rapid flow. A cutdown using a No. 320 polyethylene catheter assures rapid injection, but satisfactory results are obtained with a large bore needle. A lever type of hand injector is then connected to the needle, and 75 cubic centimeters of 85 or 90 per cent hypaque or cardiografin are rapidly injected into the antecubital vein. The duration of injection is usually 3 seconds or less. Seven seconds after completion of the injection, a single anteroposterior film is made utilizing the standard kidney, ureter, bladder technique. Shortly thereafter, a second film is taken for purposes of comparison.

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Dr. Bernstein is a Post-doctoral Research Fellow, National Heart Institute, U. S. Public Health Service.
This work was supported in part by the Squibb Institute for Medical Research, New Brunswick, New Jersey.

RESULTS

Since the technique has been developed, 25 patients have been examined by this method. In 16 cases, the visualization of the placenta was good. In 6 patients, there was fair visualization. In these cases, the exact confines of the placenta were not as well shown as in the cases classified as good, but visualization was sufficient to rule out the presence of a low implantation. In 3 cases, the visualization was poor, and the placenta could not be localized. In one of these 3, the film was of poor technical quality. In the second, marked fetal motion blurred the entire visualization of the intrauterine structures. In the third case, no reason for the failure of visualization could be ascertained. Of the total of 25 examinations, 5 cases of low implantation were demonstrated and 2 cases of placenta previa.

There were no false locations of the placenta, and the correlation between the placental site, as demonstrated by the placentogram, and the site determined at the time of delivery was 100 per cent.

DISCUSSION

The 7 second interval between completion of the injection of contrast material and exposure of the roentgenographic film was determined by trial and error. Early in the study, arm to tongue circulation times were determined by utilizing decholin. These times varied between 6 and 14 seconds in apparently normal pregnant women. There was no correlation between the decholin circulation time and the number of seconds after injection that the contrast material was found in the placental site. As noted by Hodge, the placenta is recognized by both the arterial and sinus filling phases. In the arterial phase, numerous tortuous arteries are seen in the vicinity of the placenta (Figs. 1 and 2). The sinus phase is somewhat easier to recognize,

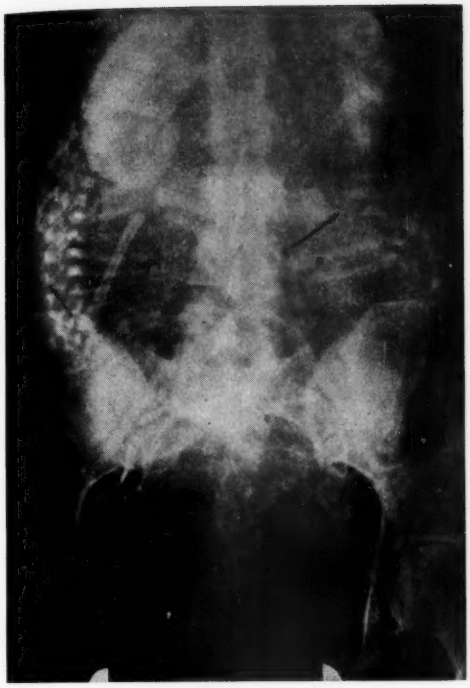


FIG. 1.

FIG. 2.

FIG. 1. Fundal implantation on the left, arterial phase.

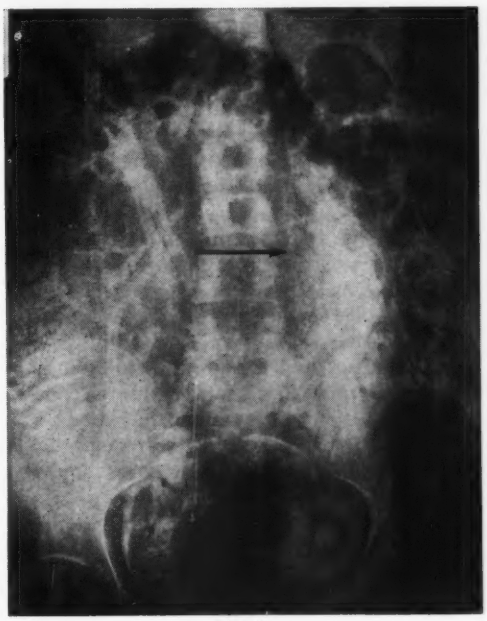
FIG. 2. Placenta previa, arterial phase.

FIG. 3. Fundal implant on the left, sinus phase.

since only blotches of radiopaque material are seen in the intervillous space, the vessels having been cleared (Figs. 3, 4, and 5). The roentgenographic appearance of contrast material in the sinus phase resembles that of a calcified placenta.

The second film is made as a base line for comparison with the study made just after injection. This comparison film is occasionally necessary, since fecal material and gas in the sigmoid colon may mimic contrast medium in the placental sinuses and cause confusion in the interpretation of the films. If this film is delayed a few minutes after the injection of contrast material, a dense pyelogram and cystogram are obtained which may further aid in confirming or ruling out the presence of placenta previa.

The rapid injection of equally large amounts of concentrated opaque material has been used by Bernstein, Greenspan, and Loken (1, 2) in over 200 cases for thoracic and abdominal aortography. The average age of their patients



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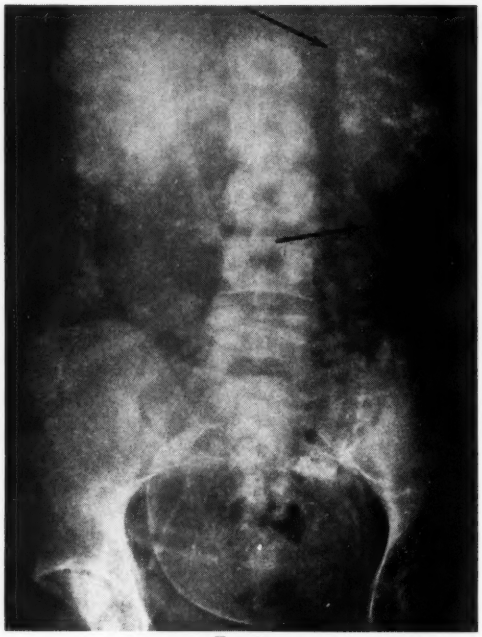

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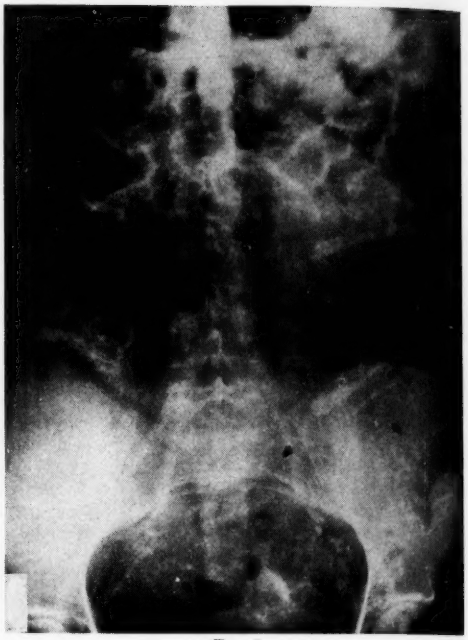

FIG. 5.

FIG. 4. Fundal implantation, sinus phase. Note large area occupied by placenta.
FIG. 5. Placenta previa, sinus phase.

has been over 60 years and many have had known arteriosclerotic heart disease. No serious reactions have been encountered. In this study, every patient had an immediate flush and described a generalized sensation of warmth lasting only a few seconds. A few of the patients have had a brief headache requiring no treatment. We have seen no evidence that the injection of this large amount of contrast material in any way affects the course of the pregnancy.

The obvious advantage of this technique is that it enables one to make a direct diagnosis as to the location of the placenta. In cases of low-lying placenta there may be some doubt as to whether a small portion overlies the cervix. Another distinct advantage of this method in comparison with soft tissue placentography is the decrease in irradiation exposure. A maximum of 2 films is required for intravenous placentography, whereas several exposures with different techniques and degrees of obliquity are often needed for soft tissue placentography.

SUMMARY

A new method for delineating the placenta is presented. This consists of the rapid intravenous injection of 75 cubic centimeters of 85 or 90 per cent hypaque or cardiografin and the exposure of a single film of the abdomen 7 seconds after completion of the injection. The procedure is accurate, safe, and simple. The use of this technique avoids excess exposure of the fetus to irradiation.

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RETROGRADE ILEOPYELOGRAPHY

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THE SURGICAL APPROACH to urinary diversion has undergone considerable modification in recent years. Cutaneous ureterostomy and ureterosigmoidostomy are used much less often than in the past. The extension of pelvic surgery to include multiple visceral resections, necessitating the accomplishment of urinary diversion in the absence of a pelvic colon, is partially responsible for the decline in popularity of the latter. In the past few years many other methods of urinary diversion have been evaluated. The isolated ileal segment has attained the greatest usage and our experience has been primarily with this procedure (2, 3).

Although it was initially performed years ago, Bricker has recently popularized the anastomosis of the ureters to an isolated segment of small intestine. Briefly, an 8 inch segment of terminal ileum, with blood supply intact, is isolated from the remainder of the intestinal tract. The proximal end of the isolated segment is closed and the distal end subsequently brought through the abdominal wall in the right lower quadrant. The ureters are anastomosed to the isolated segment and intestinal continuity is re-established. Urine drains from the ileostomy into a Rutzen-type bag.

In studying certain of these patients postoperatively, we found it useful to carry out retrograde examination of the urinary tract. In the vast majority of patients it is possible to visualize roentgenologically the isolated ileal segment, ureteroileal junction, ureters, renal pelves, and calyces (Figs. 1 and 2).

TECHNIQUE

A soft rubber urethral catheter (20 French) is threaded through a small opening in a baby bottle nipple and allowed to protrude 3 to 4 centimeters. A 20 cubic centimeter syringe containing 35 per cent diodrast (or other radiopaque medium) is attached to the catheter. A gloved finger is inserted into the ileostomy to determine the course of the last few centimeters of the isolated ileal segment. The finger is then withdrawn, and the catheter inserted until the nipple slips into the ileostomy. By exerting gentle pressure on the nipple with a hand protected by a leaded glove a "leak proof connection" is established. One may use instead a Foley catheter with the balloon partially inflated; moderate traction on the catheter prevents leakage of the contrast medium. Either method is satisfactory. With the other hand, the radiopaque medium is injected, preferably under fluoroscopic control. The course of the dye can be followed through the ileal segment into the ureters and up to the renal pelvis to outline the calyceal system. Retrograde flow seems to be facilitated by placing the patient in the Trendelenburg position. The use of the image amplifier facilitates the procedure, in that both surgeon and roentgenologist have a better appreciation of the flow of the medium.

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RESULTS

Retrograde ileopyelography, as already described, has been carried out in 25 patients in order to evaluate its feasibility and to develop a satisfactory technique. In each instance, it has been compared with intravenous pyelography. Adequate films were obtained in all but 3 patients in whom ureteral reflux did not occur. In 1 patient, lack of reflux was subsequently demonstrated to be due to ureteral compression from neoplasm. Repeat examination of the second patient 1 month later revealed slight ureteral dilatation, but intravenous pyelograms on both occasions revealed a moderate hydronephrosis. In the third patient no reflux occurred, yet intravenous pyelograms were normal. Had greater pressure been exerted ureteral filling might have occurred in the last 2 patients. Lack of reflux is not absolutely indicative of ureteral or ureteroileal obstruction, a fact which must be recognized in the evaluation of the individual case.

Several patients had one nonfunctioning kidney preoperatively as judged by intravenous pyelography. In such patients, renal function is frequently restored after urinary diversion if obstruction has not persisted beyond the point of

FIG. 1.

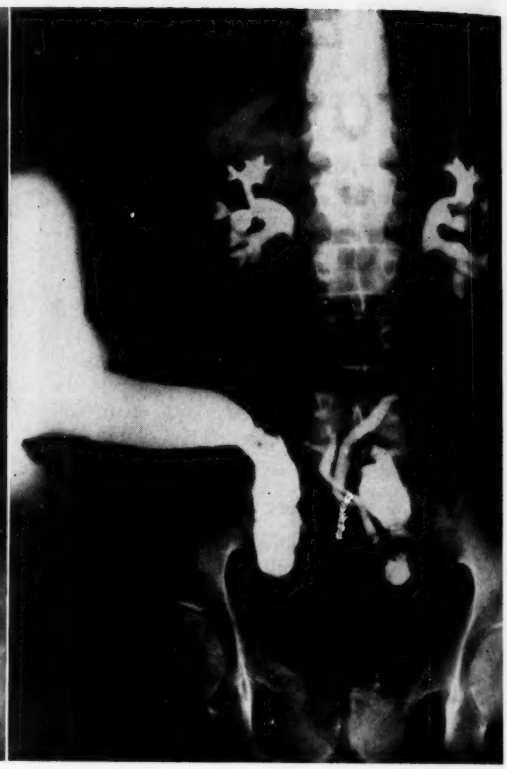

FIG. 2.

FIG. 1. A finger, protected by a lead-lined glove, prevents displacement of the catheter.
FIG. 2. Note normal appearance of renal pelves and calyces 6 months after urinary diversion.

no return. In evaluating these individuals after operation it is reassuring to find that persistent nonfunction is due to renal insufficiency rather than ureteral or ureteroileal obstruction. Reflux has occurred under such circumstances and was particularly valuable in 2 patients in whom persistent oliguria was demonstrated to be of renal origin rather than secondary to ureteral obstruction.

This procedure also demonstrates that reflux readily occurs after this method of urinary diversion. Nevertheless, renal infection has been infrequent, a fact we believe attributable to the separation of the urinary and fecal streams and to adequate drainage.

There have been no complications as a result of the procedure outlined.

Retrograde ileopyelography is not recommended in all individuals subjected to urinary diversion by "ileal bladder," but it may provide important information in the occasional patient.

SUMMARY

A technique is described which permits retrograde roentgenographic study of the ureters and renal pelves after anastomosis of the ureters to an isolated segment of ileum. Though not recommended as a routine procedure, it is of value in the study of an occasional patient with an ileal bladder.

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MIDLINE EPISIOTOMY AND EXTENSION THROUGH THE RECTAL SPHINCTER

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THE ADVANTAGES of midline episiotomy over the mediolateral type are many: (1) there is much less postpartum pain; (2) there is less bleeding and, therefore, hematoma formation is practically nonexistent; (3) secondary infection and breakdown are far less common; (4) the actual depth of the incision is less because this type is nature's episiotomy in the place where the vaginal opening should be enlarged; and (5) less suture is used in repair.

The only stated disadvantage is that if extension occurs it will be through the rectal sphincter, thus creating a complete perineotomy. Some obstetricians state that the contraindications to midline episiotomy are: (1) a thin perineal body; (2) a large baby; (3) breech presentation; and (4) a narrow pubic arch. Other obstetricians firmly state that a midline episiotomy should not be made at any time.

We believe that the advantages of midline episiotomy over the mediolateral type are so marked, particularly regarding postpartum pain—as many patients who have had both types will testify—that it more than offsets the stated disadvantages. We further believe that even if extension through the sphincter occurs, the incidence of infection, breakdown, and pain is far less frequent than with a deep mediolateral episiotomy.

MATERIALS AND METHODS

In an attempt to verify these opinions, the records of all patients who had had midline episiotomies at Methodist Hospital during the 6 year period from 1953 through 1958 were studied. During this time, there were a total number of 16,143 deliveries with 11,295 episiotomies. Of these, there were 5,358 midline episiotomies of which 109 extended through the rectal sphincter. It was noted that 5 mediolateral episiotomies also extended through the rectal sphincter, and 2 patients upon whom no episiotomy was performed, experienced complete perineal lacerations. These 109 extensions of the midline episiotomy furnish the material for this report. Some were surgical extensions to avoid impending lacerations. This procedure is preferable if complete laceration is inevitable.

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ANESTHESIA

Forty-five, 39 per cent, of these patients had general anesthesia. Seventy-one, 61 per cent, had saddle block. These figures are misleading, however, because induction of anesthesia by saddle block at Methodist Hospital outnumbers the use of general anesthetics at delivery in an excess of 5 to 1. Extension through the sphincter is relatively more common in patients delivered under general anesthesia, because of the difference in perineal relaxation.

METHOD OF REPAIR

Chromic No. 00 catgut was used almost universally. Various techniques were used but, in general, repair consisted of several interrupted sutures placed through the sphincter. The rectal wall, if involved, was repaired also by chromic No. 00 catgut, most frequently with a running lock suture but occasionally with interrupted sutures. In our opinion, the exact technique matters little as long as good hemostasis and good tissue approximation are obtained.

FINAL RESULTS

Twenty-three private physicians and 14 resident physicians composed the group attending these 109 patients. One hundred and two wounds healed by primary intention without any complications whatsoever, the postpartum course being the same as that after a simple midline episiotomy. Four patients experienced varying degrees of infection. All wounds healed completely in response to conservative treatment, antibiotics, and hot sitz baths. A fistula between the anal canal and the perineum developed in 1 patient. It healed in response to cauterization with silver nitrate. One patient experienced

fecal incontinence, and a perineorrhaphy was necessary to correct this condition. A fecal impaction developed in 1 patient during the early puerperium, probably due to edema and spasm. Digital evacuation on the third day postpartum relieved this.

DISCUSSION

From the data herein presented it would appear that even if extension through the rectal sphincter does occur it should be of little concern if properly repaired. When extension occurs, the management of repair is essentially the same as that in simple uncomplicated episiotomy. The bowels should be allowed to move, but it is wise to provide some form of stool softener. Sitz baths and perineal lamps are used just as for routine postpartum patients. If an enema is necessary it can be given after the third day. We believe that delivery under saddle block anesthesia, which provides complete perineal relaxation and allows the head to distend the perineal floor before delivery, will permit a successful midline episiotomy in almost every case.

It is thus concluded from this study that the many advantages of midline over mediolateral episiotomy make it preferable. Extension through the rectal sphincter is an infrequent complication, 2 per cent in this series of cases. If repaired properly, it is no cause for alarm.

THE SURGEON'S LIBRARY

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THE EVOLUTION OF THE MODERN SURGEON

ARTHUR S. LURIE, M.D., Peabody, Massachusetts

THE METAMORPHOSIS from barber surgeon to modern surgeon began soon after the time of Ambroise Paré and was completed by the time of Theodore Billroth. The foundations for this gradual change took place in the seventeenth and eighteenth centuries principally in France, but to a lesser degree the other countries of Europe also shared in this movement. The era of the eighteenth century which, according to Castiglione, was characterized by "individualism," "reactionary spirit," "intellectual liberalism," and "orientation toward natural and exact sciences," added the impetus to this movement.

In 1743, in France, the surgeon Peyronie (1678–1747) procured a definite, legal separation of the surgeons from the barbers. This separation was recognition of an apparent fact and of the forceful events and pressures which gradually changed the medical profession. Claude Nicolas Le Cat, who, despite the work of his biographers, is relatively unknown to the present generation of the medical profession, was one of the early physicians to contribute to this reformation and make eighteenth century French medicine and surgery outstanding.

CL^D NIC^AS LE CAT

Le Cat was born the son and grandson of local surgeons, in Bléracourt, Picardy, 6 September 1700. His early studies were at the College of Soissons, where his interests changed from philosophy and ecclesiastic studies to architecture and mathematics. However, because of his family background and ability in natural science, it seems as though he was predestined to become a surgeon. Le Cat's early training was obtained as an apprentice to his father. A formal training followed with instruction at Paris under Winslow, Peyronie, Guérin, and Morand. In 1728, he received an appointment as surgeon to Archbishop de Tressau of Rouen. He received his diploma of medicine from Reims in January 1730 and the diploma of Master of Surgery in 1732. From 1732 to 1738, Le Cat was awarded all the competitive prizes offered by the Academy of Sur-

geons of Paris. He remained in Rouen despite offers to leave and within 10 years of graduating from medical school he was appointed surgeon to the Hotel Dieu of Rouen.

Le Cat's interests and energies were many and varied. In 1738, after some initial difficulties, he was able to establish an anatomic school in Rouen. Le Cat published over 25 papers on the principles of medicine, surgery, astronomy, electricity, history, and archeology as well as approximately 70 communications in the Bulletin of the Royal Academy of Science of Rouen, which he helped establish and of which he was secretary. He was considered to be an excellent lithotomist as well as anatomist and invented several surgical instruments including a cystotome and a urethrotome.

It is known that he was one of the first to treat several patients with paralysis with electricity. It was not until the time of Duchenne (1806–1875), a century later, that more extensive use of electricity was employed in the diagnosis and treatment of nervous diseases.

In a monograph published in 1765, Le Cat described a case of jaundice with the autopsy findings.

> Pierre Poulard, aged 80, born in Fruges . . . came to our hospital in the spring of 1764 with deep jaundice, severe cachexia and fever and died on the second of July. Fifteen days before his death his yellow jaundice became black, first in his face, then gradually over the rest of his body, but less than on his face. I autopsied him on the third of July. He had at the place where the duodenum received the common and pancreatic ducts, a scirrhous, necrotic tumor, and therefore his excretory ducts were completely obstructed; from that came the reflux of the bile and pancreatic juice. The gall bladder was large and completely distended. The bile contained in this pouch was the darkest I had ever seen; at the same time it was extremely thick and very viscous. The whites of his eyes were yellow as in all cases of jaundice.

It was not until 100 years later that the French surgeon Ludwig George Courvoisier (1843–1918) formulated his famous law with reference to the gallbladder and pancreatic carcinoma.

Le Cat's correspondence carried him to other fields of medicine including case reports on spontaneous combustion, cited by Oliver, and opposition to Albrecht von Haller and his theory of sensibility and irritability. Le Cat's experiments and intellectual reasoning in refuting von Haller's theory were faulty and are critically analyzed by von Haller in a paper read at Goettingen in 1752.

At the age of 42, Le Cat married Marguerite Champossin who was 13 years, 3 months of age. Their only child, a girl, was born in 1748. His son-in-law, Jean Pierre David, succeeded him at his death. Le Cat was knighted in 1764 and died 20 August, 1768.

Claude Nicolas Le Cat lived in an age of transformations, changes, and revolutions. A learned man, versed in many branches of science, a teacher and a surgeon of reputation, he was a product of his era. Most of his writings have little value, since he frequently lapsed into philosophic theories in place of scientific reasoning and facts. Nevertheless, he is representative of the more important and enlightened surgeons of his era and helped perpetuate the evolution of the modern surgeon.

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Reviews of New Books

IN THE BOOK entitled *Fellowship of Surgeons*,[1] the history of the American College of Surgeons has been recorded in an extraordinary manner. The form of the story is not that solid, old device, the journal, but is in essence three closely related stories woven into a lively, readable book. One needs little imagination to believe that he is relaxed in front of a large open fire listening to the author recounting the life of Franklin H. Martin of Chicago and his friends; the origin, growth, and development of the American College of Surgeons; and the surprisingly rapid maturing of North American surgery. This book demonstrates very clearly how these three narratives are intimately related. The informality of the writing is deceptive; it is an authoritative account illuminated with frequent quotations from letters, addresses, and articles by the principals involved.

Franklin Martin, "practical idealist," created the journal, SURGERY, GYNECOLOGY & OBSTETRICS, in 1905 and it was successful. Martin and his associates continued their campaign for the elevation of surgical standards with the organization of the Clinical Congress of Surgeons of North America in 1910 and the American College of Surgeons in 1913. From the start, it is evident that Franklin Martin envisaged the College much as it exists today, having a significant and important influence for good in the training of surgeons, the continuing education of surgeons, and the practice of surgery. His dedication to these ideals influenced his less imaginative and less forceful colleagues to lend their help in ensuring the provision of the best possible care for the surgical patient.

The author points out that the American College of Surgeons, in the Martin era, waged a continuous battle against all influences which tended to lower the standard of surgical care in North America. Fee-splitting, kick-backs, unnecessary operations, ghost surgery, excessive fees, and itinerant surgery were attacked with varying degrees of success. This phase of the story is told with wit and humor that lightens the recital of the age-old struggle between idealistic aims and ingrained evil practices, prejudices, and misunderstandings. Doctor Davis stresses the fact that the accomplishments of the College have been primarily due to the efforts of many individuals working, not always harmoniously, together. He provides an insight into the characters of some of the most famous surgical personalities of the era.

When Martin died in 1935, he was sorely missed, and for a time the College "floundered" as might be expected when such a strong hand was missing from the "helm." Evarts Graham was elected to the Board of Regents in 1940 and Paul Hawley was appointed as Director of the American College of Surgeons in 1950, and these two men, aided and abetted by Ravdin and others, have "restated and reaffirmed" the basic principles and aims of the organization as it became necessary in facing controversial issues courageously. In this way, they have continued the basic method used by Franklin Martin and his associates in meeting each crisis in the early days of the organization.

Accomplishment and respectability are frequently accompanied by complacency; nevertheless, the author points out that the American College of Surgeons is the keeper of the conscience of North American surgery and, as such, must be ever watchful.

The book is not faultless and younger readers would have appreciated photographs of the surgical greats of the past, but on the other hand, it would have been difficult to know where to draw the line.

This story about surgery is written with assurance; the author has a nice sense of proportion, in the construction of the story, between entertainment and historical commentary. Loyal Davis has in a convincing manner shown how men of vision and courage, dedicated to an ideal, accomplished their task, and in doing so he has produced a fascinating book.

—*Walter MacKenzie.*

IN THE VOLUME entitled *Surgical Treatment of Bone and Joint Tuberculosis*[2] Roaf, Kirkaldy-Willis, and Cathro have contributed the much needed weight of large experience to a rapidly changing literature on tuberculosis of the bones and joints. The continued prevalence of tuberculosis in Africa has provided the proving ground for innovations in treatment and departures from traditional methods. The authors' experience with preantibiotic forms of treatment at the Robert Jones and Agnes Hunt Orthopedic Hospital has formed the basis for a cautious blending of old and new.

The authors have properly observed that social and economic considerations may determine the best form of treatment in a given case and that what is good for Kenya may not be best for the Western countries. This is exemplified by the authors' remark: ". . . if . . . the patient is not accustomed to wearing shoes."

The subject of diagnosis is well covered, with emphasis upon the hazard of "assuming that a diagnosis must be tuberculosis." The need for diagnosis with the aid of biopsy and culture prior to institution of specific therapy is given proper notice. The direct method of diagnosis became at the same time possible and imperative with the introduction of specific therapeutic agents. The authors support the growing belief that under antimicrobial cover tuberculous abscesses can be invaded surgically with relative impunity and that the destructive effects of the pressure of the abscess can be averted. They have adequately demonstrated, even more remarkably, that after thorough surgical de-

[1]FELLOWSHIP OF SURGEONS; A HISTORY OF THE AMERICAN COLLEGE OF SURGEONS. By Loyal Davis, M.D., F.A.C.S. 523 pages. $10.50. Springfield, Ill.: Charles C Thomas, 1960.

[2]SURGICAL TREATMENT OF BONE AND JOINT TUBERCULOSIS. By Robert Roaf, M.A., M.Ch. Orth., F.R.C.S.Ed., F.R.C.S.Eng., W. H. Kirkaldy-Willis, M.A., M.D., B.Chir., F.R.C.S.Ed., and A. J. M. Cathro, M.B., Ch.B. Foreword by Harold Boyd, M.D., F.A.C.S. Illustrations by W. Cannell, M.C.S.P. 137 pages, 90 illustrations. $7.00. Edinburgh and London: E. & S. Livingstone Ltd., 1959; Baltimore: The Williams & Wilkins Co., exclusive U. S. agents.

bridement and sequestrectomy, bone grafts can be implanted immediately. Although the grafts used by the authors occupied the site of a recent cold abscess, they survived to produce intra-articular arthrodesis. The authors have used this principle of "debridement-fusion" in all major joints with remarkable success. This approach to the treatment of tuberculosis of the spinal column seems radical, but it is only an extension of the methods of costotransversectomy and anterolateral decompression advocated by Capener, Seddon, and others. Since no mention is made of the use of laminectomy for decompression in spinal tuberculosis with paraplegia, this procedure presumably is implicitly discredited.

Surgical techniques are briefly but adequately described. These are not original, except in some cases in which they are applied to tuberculosis. The authors have used methods which have been described but are not widely known or used. One such technique is that of wide abduction arthrodesis of the hip as advocated by Abbott in 1931. Their experience with this method has been remarkably good in tuberculosis as well as in other conditions in which the femoral head has been destroyed.

This book is amply illustrated and is well printed. The diagrams are clear, the reproductions of roentgenograms are fair, and the index is adequate. The style of writing and organization of material are such that the book is easily readable. This volume is an important addition to a changing literature and should serve as a valuable guide to current thought.

—*Norman W. Hoover.*

THE EDITORS of the volume on the *Treatment of Cancer in Clinical Practice*[3] state that it was designed mainly for the interest of men and women preparing for postgraduate examinations, such as the F.R.C.S., M.R.C.O.G., and F.F.R. With this stated goal, they have enlisted outstanding surgeons and radiotherapists throughout the British Isles and have compiled a comprehensive survey of the difficult subject of cancer therapy. The chapters are succinctly written and one senses the authoritativeness.

The first 8 chapters are devoted to general subjects, with the remainder of the volume divided according to the regional distribution of cancer treatment. The first 2 chapters deal with the general principles of treatment. Then there is a chapter on the approach to surgical treatment; 2 excellent chapters on the physics and the principles and methods of radiotherapy; and chapters summarizing the important subjects of chemotherapy of cancer, hormonal control, and the presentation of results. The next 10 chapters are devoted to tumors affecting the various organs of the head and neck. This reviewer is somewhat at a loss to explain why the Editors arranged the table of contents so that the chapters dealing with the reticuloses, blood, bones and joints, and connective tissues are interspersed between chapters devoted to tumors of the head and neck. Similarly, the reason for separating tumors of the penis, male urethra, and scrotum (Chapter 38) from other tumors of the male genitalia, which include the testis and retroperitoneal region and the prostate (Chapters 29 and 30) is not clear.

The cross section of cancer therapists who have contributed to this volume includes 29 in the surgical specialties, 17 in the field of radiotherapy, 3 internists, 2 devoted to cancer research, 1 endocrinologist, and 1 statistician. Many of the contributing authors are directors of their departments and their vast experience is reflected in the presentation of the data.

To present fully the entire field of cancer therapy in a single volume is impossible; and certain chapters are weakened by a paucity of step-by-step techniques of surgical operations and radiologic methods, and some are deficient in the presentation of results. These are minor criticisms, for the Editors have definitely accomplished their goal of summarizing in this volume the present day methods—both surgical and radiologic—of treating cancer. It is interesting that a book by so many contributors reflects a relatively unified philosophy of therapy and maintains the aspect of a unified volume rather than of a collection of individual reports; the editors are to be congratulated on this accomplishment.

This book will be of value to all students, residents, and general practitioners. The specialist may find the subject of his particular field not fully presented; nevertheless, the volume is recommended to him for orientation in those fields of cancer therapy not directly related to his own field.

—*Irving M. Ariel.*

MEMBERS OF THE FACULTY of the Prosthetics Education Project in the School of Medicine at the University of California, Los Angeles, have compiled the book entitled *Prosthetic Principles—Above Knee Amputations*.[4] Much of the material contained in it is based upon research projects supported by the Office of Vocational Rehabilitation, Department of Health, Education, and Welfare, and the Veterans Administration.

The field of above-knee prosthetics is covered. Functional anatomy and locomotion are discussed in the first 43 pages, and it has been written in such a manner so that prosthetists will understand. A section of the book describes stump measurements, socket patterns, lay-out of the socket, and shaping the socket. An excellent chapter on "Biomechanics of the Amputee" is included. The remainder of the book is devoted to fitting and alignment and the details of making and adjusting the prosthesis. A short section is devoted to teaching the amputee to use the prosthesis.

The book is well illustrated, and step-by-step pictures along with the text make the procedures quite clear.

The book is of primary interest to the prosthetist, but may be useful to the surgeon concerned with amputees and to the people engaged in rehabilitation of the amputee.

—*William A. Larmon.*

[3]TREATMENT OF CANCER IN CLINICAL PRACTICE. Edited by Peter B. Kunkler, M.A., M.D.(Cantab.), M.R.C.P., F.F.R., and Anthony J. H. Rains, M.S.(Lond.), F.R.C.S. 821 pages, illustrated. $19.00. Edinburgh and London: E. & S. Livingstone Ltd., 1959; Baltimore: The Williams & Wilkins Co., exclusive U. S. agents.

[4]PROSTHETIC PRINCIPLES—ABOVE KNEE AMPUTATIONS. By Miles H. Anderson, Ed.D; John J. Bray, C.P., C.O., Charles A. Hennessy, C.P., C.O. Edited by Raymond E. Sollars. 331 pages, illustrated. $10.00. Springfield, Ill.: Charles C Thomas, 1959.

THE FIRST EDITION of the book *Lehrbuch der Gynaekologie fuer Studium und Praxis* appeared in 1922, and there has been a lapse of 14 years between the fourth edition and the present one.[5] The author, who is now Emeritus Director of the Leipzig Woman's Clinic has brought the book up-to-date. One of the striking observations is the entire omission of lists of references, either at the end of chapters or at the end of the book. Many references are given in the text, but a great many names are mentioned without references.

The author is faithful to some old forms of therapy. In the treatment of ovarian insufficiency he gives detailed instructions concerning diet, light therapy in the form of sun baths, hydrotherapy, thermotherapy, gymnastics, sitz baths, and foot baths. Several pages and 8 illustrations are devoted to the subject of acute (spitzwinklige) anteflexion of the uterus. For this anomaly, dilatation of the cervix, curettage, iodoform-glycerine-tamponade and, in selected cases, the Alexander-Adams operation have been recommended. Likewise, considerable space and several illustrations are given to retroflexion of the uterus. For this condition the author suggests the use of vaginal pessaries or operations performed inguinally, abdominally, or vaginally. He emphasizes the great importance of daily abdominal wall and back gymnastics as an aid in the treatment of retroflexion.

It was astonishing to learn that at the Leipzig Woman's Clinic among 61,086 gynecologic patients there were only 127 cases of genital tuberculosis (0.2 per cent). In the treatment of pelvic tuberculosis, Schröder recommends roentgen therapy, radium, and intracavitary therapy. There was also a very low incidence of endometriosis. The author says he cannot quote figures because the diagnosis can be accurately made in, at most, three-fourths of all the cases.

Among the 1,429 ovarian tumors observed at the Leipzig clinic, 29 per cent were carcinomas, 18.6 per cent were dermoids, and 9.1 per cent were fibromas or fibroadenomas.

The book is well written in lucid German, and the illustrations are numerous, clear, and instructive. It appears that this once very popular book will regain its previous position even though 14 years have elapsed since its last edition. —*J. P. Greenhill.*

THE BOOK *An Introduction to Gynecological Exfoliative Cytology*[6] may be better referred to as a primer. In order to understand this statement it is necessary to read the preface. Also, emphasis is placed upon the necessity to know the normal cells of the female reproductive system to become adept at screening smears.

Chapters on "Anatomy and Histology" are followed by one on "Endocrinology." All are easily readable for those who have had limited work in biology. Next there are ones defining the cell and explaining microscopy and microtechnique. The following chapters deal with exfoliative cytology and include methods of preparation of slides, descriptions of cells on the slides (including extraneous material), and epithelial cell counts in normal smears. A final brief glossary contains simple definitions of more frequently used medical terms.

The photomicrographs are in black and white. They are satisfactory and useful.

A text of this form has a definite place and may be very helpful to the beginner in cytology.

—*M. C. Wheelock.*

A SELECTION of well illustrated papers by Italian authors is contained in the volume entitled *Archivio "Putti" di chirurgia degli organi di movimento.*[7] As in previous volumes, format and illustrations are superb.

Five cases of epidermoid and dermoid tumors of the spinal canal are presented by Fineschi. Three of these tumors occurred in children. The clinical symptoms and roentgenographic pictures are described, but the exact diagnosis can often be made only at surgery.

In a paper on degenerative joint disease in rats produced with gonadotropins, Lunardo and De Bastiani explain the degenerative joint disease produced in 60 mature rats treated for a long period of time with pituitary-like follicular and luteinizing hormones. The authors conclude that the increased concentration of gonadotropin which is observed in old age may play a role in the pathogenesis of postclimateric arthrosis.

Grilli studied 71 patients with congenital syndactylia of the hand seen at the Instituto Ortopedico Toscano. The deformity was 2½ times more common in males than in females, and it was bilateral in 19 instances. The different types of syndactylia, with and without bone involvement, are discussed as well as the different theories on the teratogenic factors.

Stringa and Mignani report on their results in 27 cases of tuberculosis of the hip joint treated by extra-articular arthrodesis. At operation, a tibial cortical bone graft is tunneled through the greater trochanter into the wing of the ilium. In 71 per cent of the cases the hip joints were solidly fused in 10 months; however, only in 37 per cent were bone trabeculas seen to cross the joint.

Lazzari presents a clinical review of 1,055 patients with intervertebral disc herniation who were operated upon from 1948 to 1957. Very good results were obtained in 85 per cent of the cases. When a clear disc herniation was not found at operation the patient did not benefit.

Biochemical and histochemical studies of intervertebral disc material removed at the operation for herniated discs were carried out by Bertolin and Rodighiero. The amino sugar content of the disc material was greatly decreased in relation with the normal; whereas the total nitrogen content was found to be increased.

Mangini and Grilli found changes of stenosing tenosynovitis in the flexor tendon sheaths in the carpal tunnel in patients with the syndrome of median nerve compression in the tunnel. Mangini also reports on 3 cases of deformity of the trapeziometacarpal joint. The

[5] LEHRBUCH DER GYNAEKOLOGIE FUER STUDIUM UND PRAXIS. By Professor Dr. Med. Robert Schröder. 5th ed. 506 pages, illustrated. Leipzig: Georg Thieme, 1959.

[6] AN INTRODUCTION TO GYNECOLOGICAL EXFOLIATIVE CYTOLOGY. By Winifred Liu, M.D. 127 pages, 44 illustrations. $6.00. Springfield, Ill.: Charles C Thomas, 1959.

[7] ARCHIVIO "PUTTI" DI CHIRURGIA DEGLI ORGANI DI MOVIMENTO. Bibliographia 1956. Directed by D. Casuccio (Padova), and O. Scaglietti (Firenze). Edited by L. Gui (Bologna). Vol. XI. 447 pages, illustrated. Firenze: Edizioni Scientifische dell "Instituto Ortopedico Toscano," 1959.

condition is bilateral and is related to abnormal development of the trapezium with presence of accessory ossicles.

Rare cases of interest observed in several Italian orthopedic clinics are described at the end of the book. —*I. V. Ponseti.*

THE MONOGRAPH entitled *Arterial Embolism in the Limbs*,[8] by A. L. Jacobs of London, is an unusually intensive report of studies relating to the clinical features, pathology, and anatomy of peripheral embolism in the extremities. The clinical reports are based upon the author's personal observations of 69 patients with 122 incidents of limb embolism covering a 16 year period. In the evaluation of the etiologic factors involved, attention is directed to the influence of heart disease, cardiac arrhythmia, congestive heart failure, exertion, and digitalization.

Particular emphasis is placed upon the clinical findings as they pertain to problems in anatomic diagnosis, clinical management, and prognosis. The manner in which clinical conclusions are supported by pathologic descriptions is unique. In 34 of 48 autopsies, representing 64 extremities in which emboli to major arteries had occurred, pathologic study included injection and dissection of the peripheral vascular tree. Many postmortem arteriograms are shown in conjunction with photographs of the resected portion of the involved arteries. There may be some question as to the reliability of this method of approach in differentiating between premortem and postmortem thrombosis and subsequent alterations in vascular channels. Perhaps the most important observation of this phase of the study concerns the extent to which propagation of thrombosis distal to the embolus influences the ultimate fate of the extremity. Pathologic support is given to the conclusion that gangrene is rarely precipitated by consecutive thrombosis in an embolized limb but is determined rather by anatomic factors causing deficiency of collateral circulation.

A separate phase of the study involved the evaluation of the adequacy of potential collateral circuits following arterial occlusion at the sites commonly encountered in clinical emboli. Arterial occlusion was created in cadavers by ligature. The route and availability of collateral circulation were determined by the rate at which the radiopaque solution, injected at various pressures proximal or distal to the level of occlusion, by-passed the occluded vessel. The tendency for slow collateral flow to be associated with occlusion at particularly vulnerable sites correlated closely with the greater degrees of ischemia from embolic occlusion at these sites observed in the clinical series.

The evidence for and against the influence of arterial spasm in the clinical picture of embolism is thoroughly reviewed. Based upon the author's own observations and on a critical analysis of previous experimental and clinical data, the importance of embolic arteriospasm has been greatly exaggerated.

In the chapter on treatment of arterial embolism, Jacobs considers most of the time-honored methods of medical management to be no better and, perhaps, somewhat worse than simple protective measures. With the possible exception of anticoagulant therapy, these views appear to be well supported. Limited advice is given for embolectomy to saddle emboli and to all cases of embolism of the iliac, femoral, or axillary arteries in which signs of grave ischemia are still present 2 or more hours after the onset of symptoms. In this era of reconstructive surgery for disabling arterial occlusion, acute or chronic, many American surgeons would object to the relatively simple operation of embolectomy for those patients with operable acute embolic occlusion in a viable extremity.

To quote from the foreword by Mr. C. G. Rob: "This monograph, based upon an extensive personal experience, describes the train of events both clinical and pathological which follow embolic obstruction of the arteries of the limbs and goes a long way towards establishing a rational approach to the problem of treatment." —*Edwin J. Wylie.*

IT WAS INTENDED that *The Story of Dissection*[9] be a concise historicophilosophic account of the major scientific events and world influences involved in the development of the field of animal and human dissection. The book is not, however, a complete success.

The first chapter relates that in the various ancient civilizations, purposeful human dissections were practically nonexistent. An occasional, very limited necropsy was performed, thus establishing the beginning of forensic pathology.

The mass of evidence favors the view that human dissections were not performed on a significant scale in classical Greece. Animal dissections and vivisections were permitted. Changes in concepts concerning death, and the body and soul after death, paved the way for the Hellenists of Alexandria in the first great period of anatomic inquiry.

The dogmatists of Hellenistic Alexandria practiced human dissection and vivisection on a grandiose scale. This was the first serious approach to the study of normal and morbid human anatomy. However, the empiricists of this same period still held that dissections were not necessary.

The Roman world, likewise, believed that human dissection was unnecessary. Reference is made to the fact that most of Galen's investigations consisted of animal dissections.

The stagnant years of the Dark Ages had arrived. Christianity in its early stages hindered attempts at human dissection.

During the Renaissance the reawakening interest in anatomy centered mainly on morbid anatomic changes. Necropsies, aimed at determining the cause of death and settling forensic problems, were looked upon with favor by authorities. The incidence of dissection for teaching purposes progressed more slowly.

[8]ARTERIAL EMBOLISM IN THE LIMBS; THE CLINICAL PROBLEM AND ITS ANATOMICAL BASIS. By A. L. Jacobs, M.A., D.M. (Oxon.), F.R.C.P. Foreword by C. G. Rob, M.C., M.A., M.Chir. (Cantab.), F.R.C.S. 200 pages, illustrated. $8.00. Edinburgh and London: E. & S. Livingstone Ltd., 1959; Baltimore: The Williams & Wilkins Co., exclusive U. S. agents.

[9]THE STORY OF DISSECTION. By Jack Kevorkian, M.D. 80 pages, illustrated. $3.75. New York: Philosophical Library, Inc., 1959.

Vesalius' work finally openly challenged many of Galen's tenets.

Human dissection eventually received civil and ecclesiastic sanctions. The remaining chapters of the book, from the baroque period to the twentieth century, point out steps in the further development of anatomy and pathology.

The important technical and philosophic highlights in the development of the field of animal and human dissection have been related. However, it is very brief, covering the periods from antiquity to the twentieth century in 77 pages; and, consequently, it is fragmentary in spots. Although, apparently, intended for popular reading, it lacks the usual anecdotes that add appeal and interest. The absence of an index is a handicap to the reader. The reviewer cannot agree with the statement on the book jacket which designates this "An enthralling account of the often weird and peculiar methods used in dissection . . ."

—*Carolyn Eyster Thomas.*

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

Praktische Endokrinologie. By Prof. Dr. A. Jores and Prof. Dr. H. Nowakowski. 311 pages, illustrated. $11.80. Stuttgart: Georg Thieme Verlag, 1960.

The Intestinal Tract. Richard Paul Spencer, A.B., M.A., M.D. 411 pages, illustrated. $12.75. Springfield, Ill.: Charles C Thomas, 1960.

English for the Foreign Physician. Jose Murilo Martins, M.D. Foreword by E. Grey Dimond, M.D. 121 pages, 10 illustrations, 8 tables. $5.75. Springfield, Ill.: Charles C Thomas, 1960.

Nose and Throat Histology. By James A. Moore, M.D. 64 pages, illustrated. $7.50. New York: The Macmillan Co., 1960.

Pediatric Anesthesiology. By M. Digby Leigh, M.D., and M. Kathleen Belton, M.D. 2nd ed. 460 pages, 203 illustrations. $12.00. New York: The Macmillan Co., 1960.

A Discographical Study of Ruptured Lumbar Intervertebral Discs. By Ulf Fernstrom. 60 pages, illustrated. Stockholm: Elanders Boktryckeri Aktiebolag, 1960.

De klinische Waarde van Methyloestrenolon en Allyl-oestrenol bij menstruatie Stoornissen en bedreigde Zwangerschap. By Hermanus Willemsen. 88 pages, illustrated. Leiden: Batteljee en Terpstra, 1960.

Fermente Hormone-Vitamine und die Beziehungen dieser Wirkstoffe Zueinander. Edited by Robert Ammon and Wilhelm Dirscherl. Vol. II. 900 pages, illustrated. $32.25. Stuttgart: Georg Thieme, 1960.

Body Fluids in Surgery. By A. W. Wilkinson, Ch.M., F.R.C.S.E., F.R.C.S. 2nd ed. 276 pages, illustrated. $5.00. Edinburgh and London: E. & S. Livingstone Ltd., 1960; Baltimore: The Williams & Wilkins Co., exclusive U. S. agents.

Lehrbuch der Gynaekologie. By Prof. Dr. med. Dr. med. h.c. Heinrich Martius. 6th ed. 450 pages, 476 illustrations. $12.85. Stuttgart: Georg Thieme, 1960.

Quemaduras humanas; su tratamiento integral. By Mario Gonzalez-Ulloa, F.A.C.S., F.I.C.S., F.R.C.M. With the collaboration of Dr. Eduardo Stevens. 212 pages, illustrated. Mexico: Editorial Interamericana, S.A., 1960.

Klinische Chirurgie fuer die Praxis. By Prof. Dr. med. O. Diebold, Prof. Dr. med. H. Hunghanns, and Prof. Dr. med. L. Zukschwerdt. Vol. II. 224 pages, 96 illustrations. $10.00. Stuttgart: Georg Thieme, 1960.

The Office Assistant in Medical Practice. By Portia M. Frederick and Carol Towner. 2nd ed. 407 pages, illustrated. $5.25. Philadelphia: W. B. Saunders Co., 1960.

Nonpenetrating Injuries of the Abdomen. By Robert H. Kennedy, M.D., F.A.C.S. 120 pages. $4.75. Springfield, Ill.: Charles C Thomas, 1960.

Radiology as a Diagnostic Aid in Clinical Surgery. By Howard Middlemiss, M.D., F.F.R., D.M.R.D. 151 pages, illustrated. $7.50. Springfield, Ill.: Charles C Thomas, 1960.

Les sutures bronchiques; étude expérimentale, importance du matériel utilisé. By Carl Théodor Dahl. 111 pages, illustrated. Marseille: M. Leconte, 1960.

Nouvelle pratique chirurgicale illustrée. By Jean Quénu. 288 pages, illustrated. Paris: G. Doin & Cie, 1960.

Exposés d'anesthésiologie, a l'usage des praticiens et des étudiants. 1st series. By P. Huguenard and P. Jaquenoud. 218 pages, illustrated. Paris: Masson et Cie, 1960.

Exposés d'anesthésiologie, a l'usage des praticiens et des étudiants. 2nd series. By P. Huguenard and P. Jaquenoud. 274 pages, illustrated. Paris: Masson et Cie, 1960.

AMERICAN COLLEGE OF SURGEONS

OWEN H. WANGENSTEEN, Minneapolis, *President*

I. S. RAVDIN, Philadelphia, *President-Elect*

PRELIMINARY PLANS FOR THE 46TH CLINICAL CONGRESS CIVIC AUDITORIUM, SAN FRANCISCO, CALIFORNIA 10 TO 14 OCTOBER 1960

IN THIS ISSUE, for your advance consideration, an outline of the nine Postgraduate Courses is listed, with chairmen, moderators, lecturers, subjects, and days given. Courses will appear in full in the final program. Because seating is limited for these classes it is advisable to register for the course of your choice as quickly as possible. The fee is $5.00. Admission will be by ticket only. Official registration forms are now available from College headquarters. If you plan to come, please write immediately for these forms: American College of Surgeons, 40 East Erie Street, Chicago 11, Illinois.

Preoperative and Postoperative Care

FRASER N. GURD, Montreal, *Chairman*
Tuesday through Friday, 8:30–11:30 a.m.

PROBLEMS IN PREOPERATIVE PREPARATION
FRASER N. GURD, Montreal, Moderator.

The Rapid Preparation of the Cardiac Patient. ARTHUR SELZER, San Francisco.

The Evaluation of Pulmonary Function. JOHN M. KINNEY, Boston.

Disorders of Body Fluid Metabolism in Gastrointestinal Disease. HENRY T. RANDALL, New York.

The Patient on Prolonged Cortisone Therapy. MARK A. HAYES, New Haven.

The Newer Enzyme Determinations in Surgery. GEORGE L. NARDI, Boston.

Case Analysis Clinic. ROBERT E. L. BERRY, Ann Arbor, Presiding. Participants: JOHN M. KINNEY, HENRY T. RANDALL, and MARK A. HAYES.

PROBLEMS DURING OPERATIONS
JONATHAN E. RHOADS, Philadelphia, Moderator.

Circulatory Collapse During Operations. FIORINDO A. SIMEONE, Cleveland.

Cardiac Arrest. BEN EISEMAN, Denver.

The Protection of the Patient Against the Dissemination of Cancer Cells. TILDEN C. EVERSON, Chicago.

Acid-Base Disturbances Due to Anesthesia or Open Chest. RICHARD A. THEYE, Rochester, Minnesota.

Antibiotics During Operations: Indications and Hazards. ISIDORE COHN, JR., New Orleans.

Case Analysis Clinic. FRANCIS D. MOORE, Boston, Presiding. Participants: FIORINDO A. SIMEONE, BEN EISEMAN, and RICHARD A. THEYE.

PROBLEMS IN POSTOPERATIVE CARE
DAVID V. HABIF, New York, Moderator.

Postoperative Care in Cardiac Disease. JACK A. CANNON, Los Angeles.

Postoperative Parenteral Fluid Therapy. JAMES R. MCCORRISTON, Montreal.

Postoperative Sepsis and the Use of Antibiotics. H. ROCKE ROBERTSON, Montreal.

Shock in Man. FRANCIS D. MOORE, Boston.

Hemorrhagic States. J. GARROTT ALLEN, Palo Alto.

Case Analysis Clinic. HORACE J. MCCORKLE, San Francisco, Presiding. Participants: H. ROCKE ROBERTSON, JAMES R. MCCORRISTON, and J. GARROTT ALLEN.

SPECIAL PROBLEMS
FRANCIS D. MOORE, Boston, Moderator.

Intestinal Obstruction. ROBERT M. ZOLLINGER, Columbus.

Clinical Abnormalities of Wound Healing. PHILIP B. PRICE, Salt Lake City.

Diagnosis and Treatment of Thromboembolism. RICHARD WARREN, Boston.

The Special Care Unit. J. MURRAY BEARDSLEY, Providence.

Choice of Colloid in "Plasma" Therapy. PAUL I. HOXWORTH, Cincinnati.

Changing Concepts for Blood Transfusions. LEWIS L HAYNES, Chelsea, Massachusetts.

Gastrointestinal Disease

JOHN A. SCHILLING, Oklahoma City, *Chairman*
Tuesday through Friday, 8:30–11:30 a.m.

REGULATION OF ACID-PEPTIC SECRETION
MERLIN K. DU VAL, JR., Oklahoma City, Moderator.
Gastric Secretory Mechanisms. M. K. DU VAL, JR.
Role of Pancreaticobiliary and Intestinal Secretions. RENE B. MENGUY, Oklahoma City.
Psychological Factors. STEWART G. WOLF, JR., Oklahoma City.
Role of the Vagus Nerve. EDWARD R. WOODWARD, Gainesville.
Summation of Clinical Implications. M.K. DUVAL, JR.

GASTRIC SURGERY
LLOYD M. NYHUS, Seattle, Moderator.
Hemigastrectomy and Vagotomy. DOUGLAS A. FARMER, Boston.
Billroth I Gastrectomy. LLOYD M. NYHUS, Seattle.
Segmental Resection. DAVID STATE, New York.
Vagotomy and Gastroenterostomy. KEITH S. GRIMSON, Durham.
Postgastric Surgery Abnormalities. WILLIAM E. ABBOTT, Cleveland.

SMALL INTESTINE
PAUL R. SCHLOERB, Kansas City, Kan., Moderator.
Physiology of the Small Bowel. PAUL R. SCHLOERB.
Regional Enteritis. IVAN D. BARONOFSKY, New York.
Argentaffinoma. JOHN R. BROOKS, Boston.
Ileal Conduit. C. ALAN MCAFEE, St. Louis.
Maximal Resection—Homotransplantation. RICHARD C. LILLEHEI, Minneapolis.

INTESTINAL OBSTRUCTION
JOHN A. SCHILLING, Oklahoma City, Moderator.
Pathological Physiology. JOHN A. SCHILLING.
Use of Antibacterials and Antibiotics. ISIDORE COHN, JR., New Orleans.
Results of Intestinal Plication, Operative Techniques. DAVID GOLD, Wiesbaden, Germany.
Large Bowel Obstruction; Diagnosis and Treatment. ALBERT W. HARTMAN, JR., San Antonio.
Causes and Prevention. JOHN MORTON, Rochester, New York.

Diseases of the Liver, Biliary Tract, and Pancreas

CHARLES ECKERT, Albany, *Chairman*
Tuesday through Friday, 8:30–11:30 a.m.

DISEASES OF THE LIVER
CARL A. MOYER, St. Louis, Moderator.
Influence of Disturbances of Liver Function on Surgical Risk. CARL A. MOYER, St. Louis.
Diagnosis and Management of Subphrenic Abscess. STANLEY R. FRIESEN, Kansas City, Kansas.
Surgical Jaundice in Infancy. WILLIAM B. KIESEWETTER, Pittsburgh.
Differential Diagnosis of Intrahepatic and Extrahepatic Biliary Obstruction. CHARLES ECKERT, Albany.
Indications, Technique, and Results of Hepatic Lobectomy. JULIAN K. QUATTLEBAUM, Savannah.

PORTAL HYPERTENSION
JOHN L. MADDEN, New York, Moderator.
The Concept of Outflow Block in Portal Cirrhosis. JOHN L. MADDEN, New York.
Hemodynamic Changes in Cirrhosis. W. DEAN WARREN, Charlottesville.
Use of Splenic Pulp Pressure Determinations and Splenoportography in Surgical Management. LOUIS M. ROUSSELOT, New York.
Management of Acute Hemorrhage from Esophageal Varices. LEO V. MULLIGAN, St. Louis.
Side-to-Side Portacaval Shunts in Treatment of Ascites. C. STUART WELCH, Albany.
Bleeding Esophageal Varices in Infancy and Childhood. H. WILLIAM CLATWORTHY, JR., Columbus.
Panel Discussion: End Results of Portacaval Shunts.

GALLBLADDER AND BILE DUCTS
FRANK GLENN, New York, Moderator.
Pathogenesis of Gallstone Formation and Cholecystitis. ALFRED M. LARGE, Detroit.
Management of Acute Cholecystitis. FRANK GLENN.
Role of Cystic Duct Stump as a Cause of Postcholecystectomy Symptoms. MERLE J. BROWN, Davenport.
Pathology of the Distal Common Duct with Special Reference to Stenosing Odditis. FERNANDO PAULINO, Rio de Janeiro.
Retained Stones in the Common Bile Duct. ROBERT T. TIDRICK, Iowa City.
Strictures of the Common Bile Duct. WARREN H. COLE, Chicago.

PANCREAS
JOHN M. WAUGH, Rochester, Minnesota, Moderator.
Pathogenesis of Acute and Chronic Pancreatitis. SAMUEL R. POWERS, JR., Albany.
Surgical Treatment of Pancreatic Pseudocysts. JOHN M. WAUGH, Rochester, Minnesota.
Chronic Relapsing Pancreatitis. ALAN P. THAL, Minneapolis.
Techniques in Clinical Interpretation of Islet Cell Function. THOMAS F. FRAWLEY, Albany.
Carcinoma of the Head of the Pancreas and Terminal Bile Ducts. RICHARD L. VARCO, Minneapolis.

Cardiovascular Surgery

JOHN W. KIRKLIN, M.D., Rochester, Minnesota, *Chairman*
Tuesday through Friday, 8:30–11:30 a.m.

TECHNIQUES IN CARDIAC SURGERY
EARLE B. MAHONEY, Rochester, Minneosta, Moderator.
Transplantation of the Heart. WATTS R. WEBB, Jackson, Mississippi.

Technique of Long-Term Use of Artificial Pacemaker. ELLIOTT S. HURWITT, New York.
Surface Cooling and Inflow Stasis. F. JOHN LEWIS, Chicago.
Extracorporeal Circulation with Pump-Oxygenator. JAMES V. MALONEY, JR., Los Angeles.
Profound Hypothermia with Pump-Oxygenator. IVAN W. BROWN, JR., Durham.
Profound Hypothermia and Circulatory Arrest with Drew Technique. ARCHER S. GORDON, Los Angeles.
Panel for Questions and Answers.

ARTERIAL SURGERY
GEZA DE TAKATS, M.D., Chicago, Moderator.
Material for Arterial Replacement. W. STERLING EDWARDS III, Birmingham.
Superior Mesenteric Artery Occlusion. ROBERT S. SHAW, Boston.
Results of Resection of Abdominal Aortic Aneurysm. BROOKE ROBERTS, Philadelphia.
Prognosis of Surgical Untreated Occlusive Arterial Disease. JOHN F. FAIRBAIRN II, Rochester, Minn.
Surgical Treatment of Terminal Aortic Occlusions. ALFRED W. HUMPHRIES, Cleveland.
Surgical Treatment of Superficial Femoral Artery Occlusions. JOHN C. IVINS, Rochester, Minnesota.
Panel for Questions and Answers.

SEQUELAE OF OPEN HEART SURGERY
C. ROLLINS HANLON, M.D., St. Louis, Moderator.
Metabolic Changes. GEORGE H. A. CLOWES, JR., Cleveland.
Changes in Cardiac Function. HENRY T. BAHNSON, Baltimore.
Ventilatory Alterations. JOHN C. CALLAGHAN, Edmonton, Alberta.
Sludging Phenomena as Related to Whole Body Perfusion. DAVID M. LONG, Minneapolis.
Changes After Potassium Induced Cardiac Arrest. JAMES A. HELMSWORTH, Cincinnati.
Changes After Cardiac Arrest Induced by Simple Ischemia or by Hypothermia. NORMAN E. SHUMWAY, JR., Palo Alto.
Panel for Questions and Answers.

SURGICAL TREATMENT FOR CONGENITAL AND ACQUIRED HEART DISEASE
JOHN C. JONES, Los Angeles, Moderator.
Aortic Valve Replacement. CHARLES A. HUFNAGEL, Washington.
Mitral Valve Replacement. EARLE B. KAY, Cleveland.
Intracardiac Tumors. C. F. KITTLE, Kansas City, Kan.
Congenital Aortic Stenosis. F. HENRY ELLIS, JR., Rochester, Minnesota.
Congenital "Isolated" Pulmonary Stenosis. ALBERT STARR, Portland, Oregon.
Complete Transposition of Great Vessels. HUGH E. WILSON III, Dallas.
Anomalous Pulmonary Venous Connections. FRANK C. SPENCER, Baltimore.
Panel for Questions and Answers.

Burns and Associated Complications

CURTIS P. ARTZ, Jackson, Mississippi, *Chairman*
Tuesday through Friday, 8:30–11:30 a.m.

INITIAL CARE AND SYSTEMIC THERAPY
OLIVER COPE, Boston, Moderator.
Initial Evaluation and Treatment. JOHN H. DAVIS, JR., Cleveland.
Replacement Therapy in Adults. JAMES F. CONNELL, JR., New York.
Use of Salt Solutions. BEN J. WILSON, Grand Junction, Colorado.
Water, Electrolytes, and Colloids in Children. BOYD W. HAYNES, JR., Richmond.
Initial Local Care. JOHN D. MARTIN, JR., Atlanta.
Round Table Discussion. All Participants.

WOUND COVERAGE
TRUMAN G. BLOCKER, JR., Galveston, Moderator.
Preparation of the Wound for Grafting. STEPHEN R. LEWIS, Galveston.
Initial Excision. BRUCE G. MACMILLAN, Cincinnati.
Priorities and Methods of Coverage Including Donor Site Care and Homografting. WILFRED T. TUMBUSCH, Fort Sam Houston.
Care of the Chronic Burn. DAVID W. ROBINSON, Kansas City, Kansas.
Special Areas—Hands, Face, and Electrical Burns. FRANK MCDOWELL, St. Louis.
Round Table Discussion. All Participants.

ENDOCRINE AND METABOLIC CHANGES: NUTRITION
JAMES D. HARDY, Jackson, Mississippi, Moderator.
Endocrine Changes in Burns. DAVID M. HUME, Richmond.
Metabolic Changes in Burns. STANLEY M. LEVENSON, Washington.
Curling's Ulcer in Burns. EDWARD H. VOGEL, JR., Fort Sam Houston.
Techniques of Nutrition. WILLIAM E. ABBOTT, Cleveland.
Round Table Discussion. All Participants.

COMPLICATIONS AND REHABILITATION
W. W. ALTEMEIER, Cincinnati, Moderator.
Infection in Burns. EDWIN J. PULASKI, Fort Dix, New Jersey.
Septicemia in Burns. BENJAMIN A. BARNES, Boston.
Renal Function and Shutdown. PAUL D. DOOLAN, Oakland.
Complications of Burns in Children. TAGUE C. CHISHOLM, Minneapolis.
Rehabilitation of the Burned Patient. ROBERT M. MCCORMACK, Rochester, New York.
Round Table Discussion. All Participants.

Gynecology and Obstetrics

GEORGE E. JUDD, M.D., Los Angeles, *Chairman*
Monday through Thursday, 8:30–11:30 a.m.

PREOPERATIVE, OPERATIVE, AND POSTOPERATIVE COMPLICATIONS AND TREATMENT OF THE GYNECOLOGIC PATIENT

HAROLD K. MARSHALL, Glendale, Moderator.

Preoperative Examination and Preparation. J. G. MOORE, Los Angeles.

Emotional Preparation of the Surgical Patient. ALLAN C. BARNES, Baltimore.

Anesthesia. JOHN B. DILLON, Los Angeles.

Coagulation Defects; Operative and Postoperative. LOUIS J. LOMBARDO, JR., Los Angeles.

Bowel Preparation, Complications, and Management. ALAN P. THAL, Minneapolis.

SECOND DAY: SAME TITLE

J. HOWARD PAYNE, Los Angeles, Moderator.

Shock Mechanisms and Treatment. LEONARD ROSOFF, Los Angeles.

Pulmonary Complications. JOSEPH BOYLE, Los Angeles.

Acute Renal Failure. ALLAN G. REDEKER, Los Angeles.

Thrombophlebitis. FRANK H. LEEDS, San Francisco.

Cardiac Arrest. WILLIAM P. MIKKELSEN, Los Angeles.

GLANDULAR EPITHELIUM OF THE UTERUS

JAMES F. NOLAN, Los Angeles, Moderator.

Embryology and Histology of Endocervix and Endometrium. C. FREDERIC FLUHMANN, San Francisco.

Relationship of Uterine Bleeding to Endometrial Histology. RICHARD L. TAW, Los Angeles.

Adenoacanthoma. EDWARD G. JONES, Pomona.

Adenocarcinoma of the Endocervix. WILLIAM O. THOMAS, JR., Portland, Oregon.

Adenocarcinoma of the Endometrium. S. B. GUSBERG, New York.

UTERINE MUSCLE PHYSIOLOGY AND FUNCTION

RALPH C. BENSON, Portland, Oregon, Moderator.

Uterine Muscle Reactions (Miniature Balloon). ROBERTO CALDEYRO-BARCIA, Montevideo, Uruguay.

Uterine Muscle Reactions (Studies with Muscle Strips). HARRY S. MCGAUGHEY, JR., Charlottesville.

Use of Relaxin in Labor. WILLIAM G. SLATE, Chicago.

Induction of Labor. BERNARD J. HANLEY, Los Angeles.

Hazards and Contraindications of Induction of Labor. HARRY FIELDS, Philadelphia.

Management of Multiple Severe Injuries

FRANCIS J. COX, San Francisco, *Chairman*

Tuesday through Friday, 8:30–11:30 a.m.

METABOLIC RESPONSES OF THE BODY TO MULTIPLE SEVERE TRAUMATIC INJURY

CARLETON MATHEWSON, JR., San Francisco, Moderator.

The Adrenocortical System Response to Trauma. VINCENT C. DIRAIMONDO, San Francisco.

Biochemical Responses to the Presence of Trauma. HAROLD A. HARPER, San Francisco.

Experimental Clinical Basis for Use of Hemodialysis and Peritoneal Dialysis. P. D. DOOLAN, Oakland.

Surgical Management of Major Injury in View of the Three Fundamental Presentations. VICTOR RICHARDS, San Francisco.

MULTIPLE SEVERE INJURY PROBLEMS

J. ENGLEBERT DUNPHY, Portland, Oregon, Moderator.

The Physiology of the Severely Injured Brain. C. HUNTER SHELDEN, Pasadena.

Major Vascular Injury, Artery and Vein. GEORGE C. MORRIS, JR., Houston.

Major Injury to the Abdomen and Contents. R. KENNEDY GILCHRIST, Chicago.

Major Injury to the Thorax and Contents. PAUL W. SANGER, Charlotte.

MAJOR SOFT TISSUE INJURIES

FRANCIS E. WEST, San Diego, Moderator.

Major and Extensive Soft Tissue Injuries Complicating Skeletal Fractures. JOSEPH D. GODFREY, Buffalo.

Fractures of the Pelvic Area with Associated Soft Tissue Injury. CHARLES R. SULLIVAN, Rochester, Minnesota.

Results of Recent Investigation and Study upon the Problem of Blood Loss, Blood Volume Determination, and Associated Fluid Imbalance. RICHARD E. GARDNER, San Francisco.

Practical Approach, Use and Abuse of Blood, Use and Abuse of Supplementary Medication. WILEY F. BARKER, Los Angeles.

GENERAL SEVERE SKELETAL ORTHOPEDIC INJURIES

EDWARD T. EVANS, Minneapolis, Moderator.

Personal Experience with the Major Injury Problem. LEE RAMSEY STRAUB, New York.

Personal Experience with the Major Injury Problem. HOWARD A. SWART, Charleston, West Virginia.

Personal Experience with Major Injury Problem. CARTER R. ROWE, Boston.

Multiple Injury Skeletal Problem as It Applies Primarily to Children Under the Age of Fifteen Years. JOHN C. WILSON, JR., Los Angeles.

Surgical Aspects of Pulmonary Disease

LYMAN A. BREWER, III, Los Angeles, *Chairman*

Monday through Thursday, 1:30–4:30 p.m.

CURRENT CONCEPTS OF CARDIOPULMONARY FUNCTION IN PATIENTS UNDERGOING CHEST SURGERY

HERBERT C. MAIER, New York, Moderator.

Preoperative and Operative Considerations. FRANK F. ALLBRITTEN, JR., Kansas City, Kansas.

Physiological Problems in the Immediate Postoperative Period Following Thoracic Operations. REGINALD H. SMART, Los Angeles.

Postoperative Cardiac or Respiratory Failure; Treatment by Mechanical Respirator. FRANK C. SPENCER, Baltimore.

Physiological Principles in the Treatment of Thoracic Trauma. WILLIAM M. TUTTLE, Detroit.
Use and Abuse of Antibiotics. H. ROCKE ROBERTSON, Montreal.
Hypothermia in Chest Surgery. LYMAN A. BREWER III, Los Angeles.
Round Table Discussion. All Participants.

ADVANCES IN SURGERY OF LUNG
CAMERON HAIGHT, Ann Arbor, Moderator.
Surgical Management of Anomalies of the Lung. CAMERON HAIGHT, Ann Arbor.
Current Treatment of Pulmonary Suppurative Disease. H. BRODIE STEPHENS, San Francisco.
Present-Day Surgical Management of Pulmonary Tuberculosis. PAUL C. SAMSON, Oakland.
Tracheobronchial Reconstruction and Grafting. STIG EKESTROM and ERIC CARLENS, Stockholm, Sweden.
Prevention of Pleural Dead Space After Pulmonary Resection. LAURENCE MISCALL, New York.
Technical Advances in Pulmonary Resection. JOHN W. STRIEDER, Brookline.
Surgical Management of Complications of Staphylococcic Pneumonia. ELTON WATKINS, JR., Boston.
Round Table Discussion. All Participants.

RECENT CONTRIBUTIONS TO GENERAL THORACIC SURGERY
GEORGE H. HUMPHREYS II, New York, Moderator.
Surgical Management of Congenital Deformities of the Chest Wall. ROLLIN A. DANIEL, JR., Nashville.
Current Management of Thoracic Empyema. EDWARD M. KENT, Pittsburgh.
Present Use of Pulmonary Decortication. HIRAM T. LANGSTON, Chicago.
Surgical Management of Intrathoracic Complications of Subphrenic Infection. HERBERT D. ADAMS, Boston.
Surgery of the Thoracic Duct. RALPH D. ALLEY, Albany.
Management of Diaphragmatic Hernia. GEORGE H. HUMPHREYS II.
Round Table Discussion. All Participants.

CURRENT STATUS OF MANAGEMENT OF THORACIC NEOPLASMS
FRANK B. BERRY, Washington, Moderator.
Tumor of the Chest Wall and Pleura. F. HENRY ELLIS, JR., Rochester, Minnesota.
Bronchial Adenomas and Benign Tumors of the Lung. LAMAR SOUTTER, Boston.
Tumors of the Mediastinum. F. G. KERGIN, Toronto.
Surgery in Carcinoma of the Lung. JOHN C. JONES, Los Angeles.
Current Use of Isotopes and Chemotherapy in Lung Cancer. ANTHONY R. CURRERI, Madison, Wisconsin.
Present Status of High Voltage and Cobalt Irradiation in Carcinoma of the Lung. JOHN L. POOL, New York.
Round Table Discussion. All Participants.

Recent Advances in Pediatric Surgery

ORVAR SWENSON, Boston, *Chairman*
Tuesday through Friday, 8:30–11:30 a.m.

SURGICAL CONDITIONS OF THE CHEST, HEART, AND GREAT VESSELS
DAVID R. MURPHY, Montreal, Moderator.
Staphylococcus Pneumonia in Infancy. WILLIAM L. RIKER, Chicago.
Acquired Eventration of the Diaphragm in Infancy. HARRY C. BISHOP, Philadelphia.
Localized Pulmonary Emphysema. WILLIAM K. SIEBER, Pittsburgh.
Approach to Open-Heart Cases with Uncertain Diagnoses. RALPH A. DETERLING, JR., Boston.
Long Term Follow-Up on Division of Patent Ductus. SAMUEL R. SCHUSTER, Boston.
Early Operation for Coarctation of the Aorta. WILLIAM T. MUSTARD, Toronto.

RECENT ADVANCES IN ABDOMINAL SURGERY
CLIFFORD D. BENSON, Detroit, Moderator.
Hydramnios as an Aid in Early Diagnosis of Obstruction of the Intestinal Tract. E. THOMAS BOLES, JR., Columbus, Ohio.
Hirschsprung's Disease in the Newborn. JOHN H. FISHER, Boston.
The Management of Intussusception. MARK M. RAVITCH, Baltimore.
Cholangiography as an Aid in Diagnosing Anomalies of the Extrahepatic Biliary Tract. IRVING A. RATNER, Boston.
Bilateral Versus Unilateral Repair of Inguinal Hernia in Infancy. WILLIAM H. SNYDER, JR., Los Angeles.
End-to-End Anastomosis Versus Mikulicz Procedure for Intestinal Resection. COLIN C. FERGUSON, Winnipeg.

RECENT ADVANCES IN THE MANAGEMENT OF TUMORS OF INFANCY AND CHILDHOOD
THOMAS H. LANMAN, Boston, Moderator.
Papillary Adenocarcinoma of the Thyroid. GEORGE CRILE, JR., Cleveland.
Newer Methods of Managing Wilms' Tumor. LUTHER A. LONGINO, Boston.
Sacrococcygeal Teratoma. LAWRENCE K. PICKETT, Syracuse.
Advances in Surgical Treatment of Endocrine Tumors in Childhood. LUKE W. ABLE, Houston.
Newer Methods of Management of Neuroblastomas. SAMUEL L. CRESSON, Philadelphia.
Perfusion Treatment of Tumors in Children. KEITH REEMTSMA, New Orleans.

SOME PROBLEMS IN PEDIATRIC SURGERY
ALEXANDER H. BILL, JR., Seattle, Moderator.
Undescended Testicle. C. L. MINOR, Philadelphia.
Urological Complications in Anoplasty. IRVING A. MEEKER, JR., Los Angeles.
The Surgical Management of Omphaloceles. HERBERT E. COE, Seattle.
Ulcerative Colitis in Children. THOMAS V. SANTULLI, New York.
Portal Hypertension. FRANK RATHAUSER, Trenton.